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TO EVALUATE THE HEMODYNAMIC EFFECTS OF KETAMINE-MIDAZOLAM AND KETAMINE- DIAZEPAM COMBINATION

Anaesthesiology

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ABSTRACT

Background: Midazolam effectively maintains hemodynamic and respiratory variables even in poor risk patients. Its onset of action is quicker, and there is less individual variation in response than after the administration of diazepam. We evaluated the hemodynamic effects of ketamine - midazolam and ketamine- diazepam combination in patients undergoing elective surgeries.

Methods: The present study was carried out in 100 patients of either sex , between the age group 18-35 years belonging to ASA class I &II undergoing elective surgeries under general anesthesia. Patients were divided into 2 groups of 50 each according to combination of induction agent used. Group I included patients receiving ketamine (0.75 mg/kg) + midazolam (0.15mg/kg) and Group II receiving ketamine (0.75 mg/kg) + diazepam (0.15 mg/kg).

Results : Group I showed a significant increase in heart rate at the time of intubation $p<0.01$, which persisted up to 15 minutes of anesthesia. There was a significant increase in heart rate, systolic diastolic and mean arterial in group II (p value<0.001).

Conclusion: Midazolam a water soluble benzodiazepine is more effective than diazepam to attenuate the cardio-stimulatory response and post-operative emergence phenomena associated with ketamine.

KEYWORDS

INTRODUCTION

Intravenous anesthesia is an integral part of modern anesthesia. There has been an increased interest in the use of intravenous induction agents after the availability of new intravenous anesthetics, higher patient acceptance and concern over anesthetic gas pollution in the operating room. But till date there is no intravenous which fulfills all the characteristics of an ideal intravenous anesthetic agent.

An ideal intravenous anesthetic agent is one which has qualities like stability in solution, a long half- life, being non- irritant, giving rapid and smooth induction and recovery and with minimal side effects.

Ketamine was used is a well known intravenous agent for induction for induction and was first used by Corrsen and Domino[1]. It is especially useful in critically ill patients. However, ketamine causes cardiovascular stimulation resulting in rise in heart rate and blood pressure[3].

Benzodiazepines have been used to induce anesthesia, when cardiovascular stability is critical. Diazepam is a colorless crystalline base, insoluble in water. It is metabolized in the liver and at least two of the metabolites formed have marked pharmacological activity. It has half- life of 24 hours. On repeated administration diazepam accumulates in the body, and the effect of the drug and its metabolite take a longtime to wear off. In its conventional organic solvent form with propylene glycol, the drug is painful on injection and the venous irritation it produces is followed by a high incidence of thrombosis.

Midazolam hydrochloride (R0-21-3981), is a 1, 4- benzodiazepine derivative currently being widely used as an induction agent in anesthesia. It differs from other benzodiazepines in that, it is water soluble, has a half–life of about 2 hours and does not cause significant thrombophlebitis. In addition, while anterograde amnesia seems to be more marked, it is of shorter duration than with other benzodiazepines, effectively maintains hemodynamic and respiratory variable even in poor risk patients. It's onset of action is quicker, and there is less individual variation in response than diazepam. Midazolam when compared to diazepam has been found to reduce the incidence of dreams after ketamine administration.[2,3,4,5]

Our study was designed to evaluate the hemodynamic effects of ketamine-midazolam and ketamine- diazepam combination in patients undergoing elective surgeries.

MATERIALS AND METHOD

The present study was conducted in the Department of Anesthesiology at SMS Medical College and Group of Hospitals, Jaipur. The study was conducted on 100 un pre-medicated adult patients of either sex of ASA physical status grade I and II who underwent elective surgery under general anesthesia requiring endotracheal intubation. A pre-anesthetic check -up of all patients was carried out. Patients between the age group 18-35 years were chosen.

The patients were divided into two groups of fifty each. For induction of anesthesia, ketamine was used in dose of 0.75mg/kg after injecting midazolam or diazepam in dose of 0.15/mg/kg.

Group I: Ketamine (0.75mg/kg) + Midazolam(0.15/kg)
Group II: Ketamine(0.75mg/kg) + Diazepam (0.15/kg)

Patients were pre-oxygenated for 3 minutes after administration of 0.005mg/kg Glycopyrolate. Then injection midazolam (0.15mg/kg) and ketamine (0.75mg/kg) was given intravenously by separate syringes in Group I and diazepam (0.15mg/kg) and ketamine (0.75mg/kg)) in Group II and vecuronium bromide 0.1mg/kg in both groups for muscular relaxation. Patients were ventilated with100% oxygen and intubation was attempted at 120 -180 seconds from the time of injecting vecuronium.

Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Heart Rate (HR) were measured before induction, after induction, at the time of inflation of cuff, at 5, 10 and 15 minutes interval and thereafter till completion of the surgery.

After inflation of the endotracheal cuff, anesthesia was maintained by Halothane 1-2% and Nitrous oxide 70% in oxygen for all cases. The only adjunctive agent used was vecuronium bromide. At completion of surgery, patients were reversed with neostigmine and glycopyrolate (0.08mg/kg & 2.5mg).

In the recovery room the patients were observed for recovery, unusual behavior, level of anxiety, orientation on awakening from anesthesia pain, mood status and any side effect

RESULTS

Table 1 shows demographic profile of the patients in both the groups. Both were comparable and did not show any variation.

The patient underwent elective surgeries like general surgery (28), plastic surgery (64) and orthopedic surgeries (8) out of 100 patients.

HEART RATE

Increase in heart rate was seen in both the Groups, but the increase was more in group II which was statistically significant (p value <0.001). (Table 2)

SYSTOLIC BLOOD PRESSURE

The mean SBP in Group I decreased from baseline 113.68 ± 6.66 mmHg to 112 .08 ± 8.15, 112.48 ± 7.98 and 112.52 ± 8.27 mmHg at 5, 10, and 15 minutes respectively post intubation and was not statistically not significant (p value>0.05). While an increase in mean SBP was seen just after induction from the baseline 117.48 ± 9.41 to 129.84 ± 13.76 and remained elevated even after 15 minutes intubation. This increase in SBP was statistically significant (p<0.001). (Table 3)

DIASTOLIC BLOOD PRESSURE

The baseline Mean diastolic blood pressure in group I was 79.08 ± 6.57 and 77.28 ± 5.86 mmHg in Group II. There was an increase in mean DBP IN Group II as compared to Group I at all the time till 15 minutes post-intubation, and this was statistically significant (p<0.001). (Table 4)

MEAN ARTERIAL PRESSURE

There was a decrease in the MAP in both the groups at all the measured time periods and was statistically not significant (p value>0.05). (Table 5)

SIDE EFFECTS

Pain at the site of injection was reported in 1(2%) patient in Group I and 26(52%) reported in Group II.

No disorientation was seen in Group I while 15 patients (30%) had disorientation post – operatively for one hour. (Table 6)

DISCUSSION

In the present study, midazolam (0.15mg/kg) with ketamine (0.75mg/kg) was used as used by Paul F White.

Midazolam and Diazepam were used with ketamine to attenuate cardio-stimulatory response and unpleasant emergence reaction response associated with it.

Midazolam and diazepam have been used in various studies for the purpose of hypnosis.

In the present study midazolam effectively blocks the cardio-stimulatory response of ketamine in dose of 0.15 mg/kg.

There was a decrease in SB, DBP, MAP, & HR which was statistically not significant. Our results are in collaboration with Paul F White and Papazain et al[6]. They also reported decrease in MAP when midazolam was used with ketamine.

Strebel[7] also found no rise in mean arterial pressure when midazolam was used with ketamine than ketamine alone.

Saint Maurice[8] used midazolam and ketamine combination in children and concluded that cardiovascular stability was excellent.

In the present study Diazepam did not effectively attenuate cardio-stimulatory response of ketamine. In Group II there was a significant increase in heart rate, systolic, diastolic and mean arterial pressure after induction of anesthesia.

Kishor Gandhi[9] compared midazolam and diazepam as induction agents and concluded that the changes in pulse rate, respiratory rate, and systolic blood pressure were insignificant after both midazolam and diazepam. However, he had not used ketamine combination.

Samuelson[10] compared midazolam and diazepam hemodynamically and reported small but definite increase in heart rate and decrease in MAP with midazolam.

Cole[11] compared midazolam and diazepam after inducing both in separate patients and observed midazolam caused a SBP change less than 10 mmHg in 89% patients and increase in heart rate exceeding 10 beats per minute.

G. Segan[12] concluded that there was no clinically significant change in HR, BP after use of any of the three benzodiazepines- midazolam, lorazepam and diazepam.

Kishor Gandhi[9] observed that patients (25) who had received diazepam recorded pain on I.V injection while (2) patients in midazolam had pain on I.V injection. In our study (26) patients had pain in Group II which had received diazepam and only (1) patient in the midazolam group. While Sasse[13] studied midazolam effects in 16 pre- medicated patients and none of the patients complained of pain at site of injection during the midazolam injection.

Kanto[14], Segan[12] reported more sedation postoperatively after midazolam use. Our study produced drowsiness in10 patients post operatively as compared to diazepam group in which there were only 2 patients.

Midazolam and ketamine combination produced 100% amnesia during the intraoperative period. While with diazepam ketamine combination in 10 patients felt awareness during anesthesia.

Sardnal[15] also observed that in small doses of midazolam 0.025 mg/kg only 44% of patients were amnesic in contrast to the combination of midazolam and ketamine which caused complete amnesia for the intra-operative procedure.

Segan[12] also noted that amnesia was most marked intra-operatively in patients receiving midazolam (90%) followed by lorazepam (75%) and diazepam (36%0.

In the diazepam ketamine group 15 (30%) patients were disoriented while none was seen in the midazolam – ketamine group. White also reported disorientation while none was seen in the midazolam group.

20 (40%) patients in the diazepam – ketamine group had vivid dreams and none in the midazolam group. Cole[11] observed the incidence of post operatively vomiting with midazolam was higher than the diazepam group. Kishor[9] observed vomiting in 3 patients receiving midazolam out of 30 and 8 patients in diazepam group.

None of the patients had thrombophlebitis in the midazolam group and 7 (14%) patients had thrombophlebitis in the diazepam group.

CONCLUSION

Midazolam is more effective than diazepam to attenuate cardio-stimulatory response and post- operative emergence emergence phenomena associated with ketamine.

TABLE 1: AGE AND SEX INCIDENCE

AGE	GROUP I		TOTAL	GROUP II		TOTAL
	MALE	FEMALE		MALE	FEMALE	
18-22	15	12	27	4	6	10
23-27	6	2	8	8	2	10
28-32	4	2	6	11	4	15
33-35	8	1	9	14	1	15
TOTAL	33 (66%)	17 (34%)	50	37 (74%)	13 (26%)	50

TABLE 2: MEAN CHANGE IN HEART RATE FROM BASELINE TO DIFFERENT LEVELS IN GROUP I & II

	GROUP I			GROUP II		
	Mean Change	S. D.	P Value	Mean Change	S. D.	P Value
Baseline	82.46	± 12.04		80.76	± 10.02	
Induction	-0.66	± 8.93	>0.05	7.56	± 5.24	<0.001
Intubation	2.14	± 6.64	<0.05	11.24	± 5.84	<0.001
5 Min.	2.78	± 6.81	<0.01	12.96	± 7.09	<0.001
10 Min.	2.9	± 6.31	<0.01	12.8	± 7.31	<0.001
15 Min.	2.86	± 6.68	<0.01	12.16	± 7.38	<0.001

TABLE 3 COMPARISON CHANGES IN SYSTOLIC BLOOD PRESSURE IN MMHG IN BOTH GROUPS WITH STATISTICAL SIGNIFICANCE SYSTOLIC BLOOD PRESSURE

	Group I		Group II	
	SYSTOLIC B.P. WITH S.D.	P Value	SYSTOLIC B.P. WITH S.D.	P Value
Base Line	113 ± 6.66	-	117.48 ± 9.41	-
Induction	-0.4 ± 5.33	> 0.05	12.36 ± 11.91	<0.01
Intubation	- 0.6 ± 6.20	> 0.05	13.28 ± 10.59	<0.01
5 Min	- 0.6 ± 6.20	> 0.05	14.28 ± 10.60	<0.01
10 Min	- 1.2 ± 6.27	> 0.05	13.48 ± 9.82	<0.01
15 Min	- 1.16 ± 6.60	> 0.05	2.72 ± 9.33	<0.01

Table 4 Comparison Changes in Diastolic Blood Pressure in mmHg in both Groups with Statistical Significance

	Diastolic Blood Pressure			
	Group I		Group II	
Baseline	79.08 ± 6.57	-	77.28 ± 5.86	-
Induction	- 0.76 ± 4.14	>0.05	4.78 ± 6.85	<0.001
Intubation	0.72 ± 4.23	>0.05	± 13.28 ±	<0.001
5 Min	-0.8 ± 4.26	>0.05	4.72 ± 6.64	<0.001
10 Min	-0.76 ± 4.22	>0.05	4.8 ± 6.65	<0.001
15 Min	-0.4 ± 4.91	>0.05	4.76 ± 6.72	<0.001

Table 5 Comparison of Mean Changes in Mean Arterial Pressure in Group I and II

	Group I			Group II		
	Mean Changes	S.D.	P. Value	Mean Changes	S.D.	P. Value
Base Line	90.24	± 5.31	-	90.45	± 6.06	-
Induction	- 0.4	± 2.63	> 0.05	7.52	± 6.00	< 0.001
Intubation	- 0.46	± 3.25	> 0.05	8.47	± 5.55	< 0.001
After 5 Min.	- 0.33	± 3.21	> 0.05	7.80	± 6.09	< 0.001
After 10 Min	- 0.45	± 3.05	> 0.05	7.71	± 6.50	< 0.001
After 15 Min	- 0.46	± 3.16	>0.05	7.25	± 6.60	< 0.001

Table 6 Side Effects in Group I and Group II

	Ketamine + Midazolam	Ketamine + Diazepam
Number of patients	50	50
Pain at I.V. Site (at the time of injection)	1 (2%)	26 (52%)
Disorientation	-	15 (30%)
Dreaming	-	20 (40%)
Drowsy	10 (20%)	2 (4%)
Intraoperative Awareness	(0%)	10 (20%)
Vomiting	2 (4%)	-
Thrombophlebitis	2 (4%)	2 (4%)

REFERENCES

1. Corssen G., Domino E. F. (1966). Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth. Analg. 45, 29–40.
2. Barker I, Butchart DGM, Gibson J, Lawson JI, M and Mackenzie N: Comparison of midazolam and diazepam. BJA, (1986).
3. Clyburn P, Kay NH and Mekenjie PT; Effects of diazepam and midazolam on recovery from anesthesia in outpatients. BJA (1986, 58, 872-875).
4. Dundee JW and Samuel. Midazolam: A water soluble benzodiazepine. Anaesthesia (1980), vol .35, 454-458.
5. Reves JG, Guenter Corssen: Comparison of two benzodiazepines for anaesthesia induction: midazolam and diazepam. Canad. Anaesth Soc. J. vol. 25, No.3, May 1978.
6. Paul F White: Comparative evaluation of intravenous agents for rapid sequence induction – Thiopentone, Ketamine and Midazolam. Anesthesiology (1982), 57: 289-282.
7. S. Strebel, M. Kaufmann, L. Maire, HG Schaefer. Effects of ketamine on cerebral blood flow velocity in humans. Influence of pre-treatment with midazolam or esmolol. Anaesthesia, March 1995, vol. 50, issue 3, pages 223-228.
8. Maurice Saint C., Landais A. The use of midazolam in diagnostic short surgical procedures in children. BJA (1990) 39-41.
9. Gandhi Kishore P.K.- Midazolam in paediatric anaesthesia: Comparison with Diazepam. Indian J. of Anaesthesia (1990)38, 155.
10. Schittze Sasse V., Hess W: Hemodynamic responses to induction of anaesthesia using midazolam in cardiac surgical patients. BJA (1982) 54, 1053.
11. Samuelson P.N, Reeves J.G.: Midazolam versus Diazepam: Hemodynamic comparison. Anesthesiology (1986) V 57, No. 5, sept.
12. Cole W.H.J: Midazolam in paediatric Anaesthesia. Anaesth. Intens.Care(1982) 10,36
13. Salonen Markker, Kanto Jusst,: Midazolam as an induction agent in children . Anesth. Analg. (1987); 66: 625-628.
14. Segan G, Dev. N. Diazepam, Lorazepam and Midazolam as pre- medicants. Indian J. Anesthesiology (1992) 40, 165.
15. Kanto J., Sjovall S., Vuori A. Effect of different kinds of pre-medication on the induction properties of Midazolam. BJA (1982), 54, 507-511.
16. SardnalF., Midazolam and Flumazenil in ophthalmology. Anaesthesia Scand (1990: 34 Supplementary 92: 35-38.