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ASSESSMENT AND COMPARISON OF EFFICACY OF MIDAZOLAM AND DIAZEPAM AS PREOPERATIVE MEDICATION

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ABSTRACT: Objective: To compare the drugs: Midazolam and diazepam as preoperative medication. **Materials and methods:** 100 patients aged between 18-60, scheduled for elective surgery were included in this comparative study. Patients were randomly allocated into two groups of 50 each. Materials and methods: Patients received 0.08mg/kg body weight midazolam inject intramuscularly and diazepam 10 mg orally. Assessment of efficacy variables: anxiety, sedation and anterograde amnesia were rated before and after drug administration (at 15, 30 and 60 minutes after drug administration) before surgery. **Finidings:** It was found that there was significant difference in mean anxiety reduction ($p<0.001$). Immediately before taking to operation theatre *i.e*. 60 minutes after drug administration, 5 with diazepam and 13 with midazolam were highly sedated. Midazolam demonstrated the better sedative, amnesic and anti anxiety effects than diazepam. **Conclusion:** With respect to anxiolytic, sedative and anterograde amnesic properties, midazolam (0.08mg/kg intramuscularly) is better premedicant compared to diazepam (oral 10 mg) for patients at preoperative period. Diazepam is also a good premedicant and use of both drugs is safe regarding cardiovascular variables and related side effects.

INTRODUCTION: Preoperative medication refers to the use of drugs before anesthesia to make it more pleasant and safe.[1] The purposes of preoperative medication are to prevent psychic shock, to regulate metabolism, elimination of any stage of excitement, and the possibility of maintaining a lighter degree of anesthesia or of using a less toxic anesthetic than would otherwise be required. [2]

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The majority of patients admitted to hospital for elective surgery experience anxiety preoperatively which can adversely influence the surgical procedure as well as the patient's recovery. Reduction of anxiety and fear at preoperative period in patients of elective surgery is essential for surgical preparation. Drugs of different classes like sedative- antianxiety drugs, opioids, anticholinergics, neuroleptics, H_2 blocker and antiemetics have been used for premedication.[3, 4] Preoperative treatments also aims at reducing the emergence agitation occurring during recovery.[5]

The comparison between the use of midazolam and diazepam as preoperative medication has been studied over different countries: USA, India, Iran and many other countries, midazolam found to

provide pre operative sedative effect superior to that of diazepam.

As diazepam is insoluble in water and pain may occur on intramuscular or intravenous injection hence, it is preferred oral route. The physicochemical properties of the midazolam allow for its water solubility and given intramuscularly [6] given to patients undergoing elective surgery. The effectiveness of anxiolytic premedication critically dependent on the anesthesist's ability to detect anxiety during the preoperative visit. This evaluation provides the frequency of the use of diazepam or midazolam as preoperative medication in the elective surgeries.

Methods:

The study was carried out in series of 100 consecutive, unselected patients, aged 18 – 60 years, admitted for the elective surgery after obtaining written consent, in College of Medical Sciences (COMS), Bharatpur, Chitwan. Patients receiving midazolam or diazepam as preoperative medication were taken and this study was carried out from the month of April to September, 2013.

Patients of either sex, different ages with mild to moderate systemic disease; all the patients for elective surgery were taken as subject. Exclusion criteria were pregnant or lactating females, patients with decompensate hepatic or renal disease, those unable or unwilling to give informed consent, hypersensitive to or had contraindications to the use of benzodiazepines or any CNS depressant for any reason, history of alcohol, benzodiazepines or other drug abuse.

Fifty patients were premedicated with diazepam (10 mg) orally one and half hour before surgery and 50 patients were premedicated with midazolam (0.08 mg/kg body weight) intramuscularly. The assessment of anxiety and vital signs were done immediately before drug administration. The vital signs were recorded before and after drug administration at various intervals i.e. at 15 minutes, at 30 minutes, and 60 minutes. These efficacy assessments like anxiety and sedation were done after drug administration at various assessment points. However the anterograde amnesia was assessed after 24 hours of premedication.

Sedation, Anxiety, and Anterograde amnesia were assessed and compared between two premedicants. The assessments were done immediately before drug administration and up to one hour after drug administration in both the cases.

General evaluation of the quality of premedication was made 24 hours after premedication. The safety variables were respiratory rate; heart rate and blood pressure before and after the drug administration were assessed five minutes before drug administration and 15 minutes, 30 minutes, and 60 minutes after drug administration. Patients were brought to the preoperative area one and half hour prior the scheduled time of surgery and the vital signs were assessed manually and anxiety was scored using VAS, sedation was scored by using Ramsay sedation scale and anterograde amnesia by asking preoperative events after 24 hours.

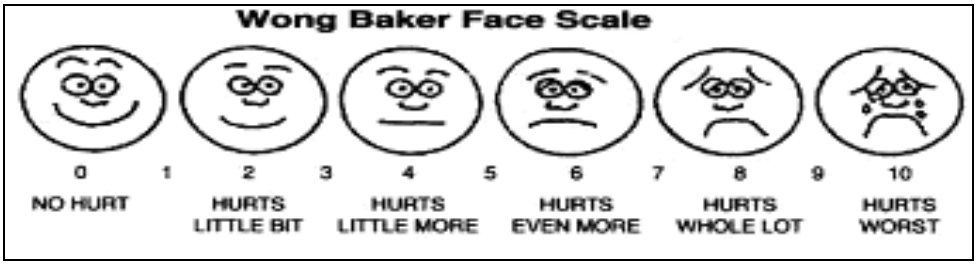
Sedation: To rate the sedation after the drug administration, Ramsay Sedation Scale (RSS) was used. The RSS is a simple scale, scored from 1 (patient anxious and agitated or restless or both) to 6 (no response to light glabellar tap). [7, 8]

Ramsay sedation scale: [8]

Sedation level	Description
1	Anxious and agitated
2	Cooperative, tranquil, oriented
3	Responds only to verbal commands
4	Asleep with brisk response to light stimulation
5	Asleep without response to light stimulation
6	Non responsive

Anxiety: To rate the anxiety before surgery, VAS was used. A VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount (categorization of none, mild, moderate and severe) of pain. [7]

Visual Analogue Scale (VAS):



0 2 4 6 8 10

FIG. 1: VISUAL ANALOGUE SCALE [7]

Anterograde Amnesia: Anterograde amnesia was rated by asking some of the preoperative events. Patients were asked if they remembered:

Being taken into the operation : A

Being shown the surgical light and : B

Being shifted from stretcher to the operating table: C

Data was recorded on predesigned proforma and statistical analysis (student's 't' test and chi square test) was done to carry out the output. Data were expressed in mean, SD and percentage. The value $p<0.05$ was considered to be statistically significant. Statician from department of community medicine was consulted for the analysis. Statistical analysis was done using SPSS software version 17.0.

RESULT: In this observational study, 100 (50 in each group) patients were taken. The mean age of the group midazolam and diazepam is 33.5 years and 37.42 years respectively. Anxiety was rated by patients themselves on a VAS and sedation using Ramsay sedation scale before the administration and after the drug administration at various time points (at 15 minutes, 30 minutes, and 60 minutes). There were no significant differences between two groups with respect to blood pressure and heart rate before and after drug administration. But there were significant differences between the groups with respect to heart rate at various time intervals after drug administration. Anxiety reduction from baseline at various time intervals was found to be statistically significant. While evaluating mean anxiety reduction only, mean reduction is greater in the midazolam group compared to that of diazepam at all the time points. (**Table 1**)

TABLE 1: MEAN ANXIETY SCORE REDUCTION FROM BASELINE WITH DIAZEPAM AND MIDAZOLAM (MEAN±SD)

Time in minutes	Diazepam	Midazolam	P value
15	13.40±8.234	17.80±7.154	0.005
30	26.40±9.370	35.40±9.026	<0.0001
60	41.80±8.792	48.70±9.836	<0.0001

Patients receiving midazolam were found to be less anxious, tranquil, cooperative and asleep without response to light stimulation whereas in case of diazepam group, majority of the patients were agitated. Unlike diazepam, desired sedation level was achieved with midazolam. (**Table 2**)

TABLE 2: ASSESSMENT OF SEDATION NUMBER PATIENT AT VARIOUS INTERVALS AFTER DRUG ADMINISTRATION:

Sedation level	After drug administration					
	15 minutes		30 minutes		60 minutes	
	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam
1	25	1	17	2	7	0
2	18	6	8	0	7	0
3	4	23	7	20	23	8
4	1	7	4	11	8	29
5	2	13	4	17	5	13
6	0	0	0	0	0	0
P value	<0.001		<0.001		<0.001	

TABLE 3: ASSESSMENT OF ANTEROGRADE AMNESIA

	Administered drug				
	Diazepam		Midazolam		p- value
Preoperative events	Yes	No	Yes	No	
Being taken into operation theatre	40	10	24	26	0.001
Being shifted from stretcher to the operation table	38	12	12	38	< 0.05
Being shown operation theatre surgical light	43	7	16	34	< 0.05

In the diazepam group greater number of patients could recall preoperative events. In midazolam group, unlike greater number of patients could not recall the same preoperative events. (**Table 3**)

TABLE 4: CHANGES IN BLOOD PRESSURE, HEART RATE AND RESPIRATORY RATE (MEAN±SD)

Vital signs	Midazolam	Diazepam	P- value
Systolic blood pressure	111.70 ±11.763	114.20 ±14.55	NS
Before drug administration			
15 min after drug administration	106.60±9.817	111.08±11.002	0.033
30 min after drug administration	100.50±9.16	106.66±10.834	0.002
60 min after drug administration	98.50±8.406	102.02±10.139	NS
Diastolic blood pressure	73.40±8.3	74.40±11.287	NS
Before drug administration			
15 min after drug administration	70.70±7.35	72.46±10.338	NS
30 min after drug administration	69.20±5.675	70.02±8.356	NS
60 min after drug administration	66.60±4.89	68.00±7.423	NS
Heart rate	75.20±6.606	74.94±7.547	NS
Before drug administration			
15 min after drug administration	75.22±5.705	80.10±9.70	0.008
30 min after drug administration	73.18±5.815	77.74±8.88	0.008
60 min after drug administration	71.12±5.306	74.64±8.201	0.028
Respiratory rate	20.58±1.691	20.38±2.079	NS
Before drug administration			
15 min after drug administration	19.42±1.739	19.42±1.842	NS
30 min after drug administration	18.70±1.741	19.04±1.628	NS
60 min after drug administration	18.58±6.158	19.00±1.484	NS

There were no significant differences between two groups with respect to diastolic blood pressure and respiratory rate before and after drug administration. However, the data showed systolic blood pressure was significantly lower in the midazolam group than in the diazepam group at 15 minutes and 30 minutes after drug administration. It was found that there were significant differences between the groups with respect to heart rate at various time intervals after drug administration.

DISCUSSION: Previous studies have shown that intramuscular midazolam is a good preoperative medicant superior to diazepam. Since diazepam: the prototype BZDs, administered intramuscularly is erratically absorbed and has poor local tolerability at the site of injection, oral diazepam is widely used by many anesthesiologist in Nepal for premedication. It was therefore considered appropriate to study intramuscular midazolam in comparison with oral diazepam for premedication.

This present study drew inference that intramuscularly injected midazolam is more effective in reducing anxiety, shows better sedation and anterograde amnesia.

While examining mean anxiety reduction between two groups (midazolam and diazepam), it showed that midazolam has higher mean reduction value from baseline at various time periods (15 minutes, 30 minutes, and 60 minutes). Midazolam showed better antianxiety effect and sedative effect compared to diazepam. This study also showed that intramuscular midazolam rapidly produces an appropriate degree of sedation and better quality of sedation than diazepam in patients awaiting surgery. The better amnesic effects of midazolam compared to diazepam have been reported. [9] Diminished recalls of events associated with surgical procedure is highly desirable property of drugs used for preoperative medication.

Diatta B. *et al.* report that midazolam as compared with diazepam can be regarded as a superior intramuscular premedicant which was similar to the present study. In his report there were no significant differences between both groups concerning heat rate, blood pressure as in my study. There was significant differences with respect to anxiety after 30 minutes 100% patients after midazolam and 67% after diazepam sedation of anxiety as noted and 63% after midazolam and 13% after diazepam were good sedated which was similar to my study (10%with diazepam and 26% with midazolam are highly sedated. Amnesia related preoperative period was more frequent in the midazolam group than in diazepam group: 67%versus 13% ($p<0.001$). [10] Likewise my study showed that midazolam has much more amnesic effects than diazepam ($p<0.001$).

Kaviani N. *et al.* conducted a prospective study on effect of oral midazolam premedication on children's cooperation before general anesthesia in pediatric surgery. In the study 0.5mg/kg of midazolam is given to children of test group and no medication to the control gropu. The study found that 0.5mg/kg midazolam premedication is effective premedicant for comfortable separation of children from parents. [11]

Mazareth M. *et al.* studied to determine the optimal method of sedation ensuring adequate preoperative sedation and anxiolysis.[12] In this case, either intranasal midazolam 0.3mg/kg, 30 minute prior to induction of general anesthesia or oral promethazine surup 1mg/kg, 90 minute prior to induction of general anesthesia was given to chosen children undergoing elective surgery. The study concluded that either midazolam or promethazine may be used as premedication as both of them are efficacious drugs.

In another study by Tripathy HK, comparative evaluation of clonidine as pediatric oral premedication, oral midazolam 0.5mg/kg and oral clonidine 5mcg/kg was compared as a premedication in pediatric patients. It was concluded that oral midazolam is a better premedication than clonidine in children in preoperative period while clonidine is better medication postoperatively.[13]

The study carried out by Gart MS *et al.* in which the examined the safety and efficacy of breast implant procedures performed under conscious sedation using protocol of preoperative intravenous diazepam, intravenous midazolam, fentanyl and local anesthetics. The study demonstrated that higher preoperative doses of diazepam have significantly reduced fentanyl requirement, shorter recovery times, decreased postoperative nausea/vomiting and elimination of unintended admissions compared to midazolam.[14]

Doyun Kim *et al*. studied on the other benzodiazepines alprazolam and triazolam alternative to midazolam. Similar to the study of mine, he evaluated anxiety, sedation and amnesic properties of benzodiazepines (alprazolam and triazolam). In his study, patients randomly received oral triazolam 0.25mg or alprazolam 0.5mg 1 hour prior to surgery and a structured assessment interview was performed in the operating room, recovery room and ward. The study concluded that there were no significant differences between two groups with respect to anxiety and sedation but amnesic property was seen in triazolam treated patients but not by alprazolam treated patients.[15]

White PF *et al*. conducted a study in which midazolam (0.5 mg /kg IV) was found to produce a spectrum of central nervous system activity like sedation and amnesia that was similar to diazepam (0.1-0.3 mg/kg IV). However the slope of midazolam dose response curve for sedation appears to be steeper. While comparing their relative sedative-amnesic property and recovery characteristics, the median effective doses of two BZDs, midazolam (0.1 mg/kg IV) found to produce profound sedation and amnesia than diazepam (0.2mg/kg IV). Patients' acceptance was higher with midazolam compared to diazepam. [16]

Atsushi Tsukamoto *et al*. carried out effect of midazolam and butorphanol premedication on inhalant isoflurane anesthesia in mice. In this study 34 male mice received either isoflurane alone or isoflurane with intraperitoneal midazolam and butorphanol premedication. The study inferred that premedication with midazolam and butorphanol was more effective in mitigation of repiratory

depression induced by isoflurane with rapid induction and fewer clinical reactions.[17]

The present study showed that intramuscular midazolam administered at the dose of 0.08 mcg/kg body weight is a suitable premedicant with better anxiolytic, sedative and anterograde amnesic effects compared to oral diazepam. Intramuscularly injected midazolam showed effects rapidly and generally within 15 minutes after administration. Diazepam, in contrast, had a delayed onset of action. Adequate anxiolytic and sedative effects were found to persist for long period about 1 and half hour after drug administration.

The local tolerability of midazolam injection in this study was better than in a published study in which 4% incidence of pain or tenderness or erythema at the site of injection was reported. [18, 19] Local tolerability of midazolam was excellent, there being no erythema, pain or tenderness at the site of injection 24 hours after injection.

CONCLUSION: The inference drawn by the present study is that intramuscularly administered midazolam produced superior anxiolysis, sedation and anterograde amnesia compared to orally administered diazepam. These agents reduced the cardiovascular activities and respiratory rate but there is no any clinical significant changes in these variables.

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