

Original Research Article

Benzodiazepine premedication in general anaesthesia: a clinical comparative study

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ABSTRACT

Background: The main aims of pre-anaesthetic medication are anxiolysis, analgesia, anti-emesis and reducing perioperative patient risk. Producing a state of amnesia for pre and post-operative events is desired by all. This study has been undertaken to evaluate the role of three of the benzodiazepines i.e. diazepam, lorazepam and midazolam during general anaesthesia, in providing anxiolysis, sedation and amnesia.

Methods: The study included patients with ASA grade I and ASA grade II physical status of both sexes, age ranging between 18-60 years. Patients were divided into three groups of thirty patients each, every group receiving intramuscular injections of diazepam 0.1 mg/kg body weight, lorazepam 0.07 mg/kg body weight and midazolam 0.08 mg/kg body weight respectively; 45 minutes prior to induction of general anaesthesia. Anxiety assessment before premedication along with assessment of sedation after premedication was done.

Results: Before premedication the mean values of pulse rate, blood pressure and respiratory rate were not significantly different among the three groups ($p > 0.05$). Maximum changes in these parameters were observed with Midazolam followed by lorazepam and diazepam. The dose of thiopentone used as inducing agent was also lowered significantly in case of midazolam ($p < 0.05$). One patient in midazolam group showed respiratory depression whereas four patients receiving lorazepam and diazepam showed delayed recovery and prolonged sedation, but the effects were self-limiting.

Conclusions: Midazolam offers the maximum advantage in allaying anxiety and providing excellent sedation and amnesia during general anaesthesia and proves to be the most suitable premedicant before general anaesthesia.

Keywords: Amnesia, Anxiety, Diazepam, Lorazepam, Midazolam, Premedication, Sedation

INTRODUCTION

The term pre-anaesthetic medication refers to drugs administered before the induction of anaesthesia to influence the course of anaesthesia. The main aims of pre-anaesthetic medication are anxiolysis, analgesia, anti-emesis and to reduce any perioperative risk to the patient.¹ The production of sedation and amnesia is related to this goal. Premedication, though is the first

stage of anaesthesia, its effects persisting throughout the period of surgery into the post-operative phase.

Anxiety is common amongst patients awaiting general anaesthesia. Incidence of anxiety has been found variable in different studies. Overall rate of anxiety was observed in 72.7% (112/154) patients scheduled for elective caesarian section.² Around 23.4% patients were found to be anxious regarding GA and females showed a higher

incidence of anxiety (35.1%) than males (11.1%) and the incidence is high in those having lower educational level.³ Human emotions like acute emotional arousal increases sympathetic activity.⁴

The word “sedation” is derived from the Latin verb *sedare* (to settle); a sedative is a drug which tends to soothe. Sedation is a state in which pre-existing anxiety is relieved or lessened, or in which signs of anxiety do not develop in circumstances in which they would normally be expected to do so. Sedation results in diminished mental activity so that mental responses to external stimuli are decreased.

The desire to produce a state of amnesia for pre-operative and post-operative events is common to all and is often helpful.

To evaluate premedication in a broader sense is a vast study. It encompasses a variety of drugs used pre operatively e.g. anxiolytics, sedatives, anticholinergics, hypnotics, antiemetics, antihistamines, opioids, H2 receptor blockers, etc. Development of the benzodiazepine group of drugs has given the anaesthesiologists a variety of interesting agents with different characteristics.

This study has been undertaken with a view to evaluate the use of three of the benzodiazepines i.e. diazepam, lorazepam and midazolam during general anaesthesia, their role in providing anxiolysis, sedation and amnesia. Their comparative efficacy regarding onset, duration and degree of sedation and amnesia during surgery under general anaesthesia is proposed to be assessed in this project.

METHODS

This study has been carried out on ninety patients undergoing various types of elective surgery requiring general anaesthesia, in the departments of general surgery, orthopaedics, urology, Gauhati Medical College and Hospital, Guwahati, during the period from August 2015 to July 2016.

The study included patients with ASA grade I and ASA grade II physical status of both sex and age ranging between 18-60 years. Patients with mild to moderate hypertension, those who seemed to be anxious and were undergoing surgery for the first time were included in the study. Patients with chronic obstructive pulmonary disease, hepatic or renal diseases were excluded from the study. Patients with history of allergy to the study drugs or anaesthetic agents, patients on treatment with antidepressant drugs or antipsychotic drugs were also excluded from the study. The ninety patients were divided into three groups of thirty patients each. After obtaining institutional approval, written and informed consent was taken from each of the patients. Randomization was done using an online tool.

Patients in the three groups I, II and III received through intramuscular route, diazepam 0.1 mg/kg body weight, lorazepam 0.07 mg/kg body weight and midazolam 0.08 mg/kg body weight respectively; 45 minutes prior to induction of general anaesthesia.

Pre-anesthetic checkup was done in the previous evening and the patients were explained in detail about the operative procedure, anesthetic technique and post-operative monitoring. The patients and their guardians were properly counseled for their cooperation.

Methods of observation

Assessment of sedation was made by grading from grade 1 (too much sedation so as to impair arousability) to grade 6 (no sedation at all) as per Vinik et al.⁵

- Hyperactive-6
- Awake/alert-5
- Awake but drowsy-4
- Asleep but easily arousable-3
- Asleep but arousable with difficulty on verbal commands-2
- Asleep and not arousable by verbal commands-1

Assessment of anxiety before medication based on observation of facial expression, pulse rate, blood pressure, sweating and preparedness to undergo surgery.

Preoperative anxiety was graded as absent/mild/moderate/marked as per Dundee et al with slight modification.⁶

- Absent-no change in any of the above parameters.
- Mild-change in any one of the above parameters.
- Moderate-change in any two of the above parameters.
- Marked-change in more than two of the above parameters.

Assessment of anxiolysis after medication was graded as excellent/good/fair/poor depending on the above parameters. Amnesia was assessed after recovery by enquiring from the patient whether he or she remembers the colour or number of memory cards shown before the operation, journey to the operation theatre or any conversation in the operation theatre prior to induction.

Requirement of the dose of the inducing agent (thiopentone sodium) was recorded. Side effects if any were also recorded.

On the day of operation, weight of the patient along with pulse rate, blood pressure was recorded. The patient was made to lie down on an isolated bed in the pre anaesthetic room, peripheral IV access with 18 G cannula was obtained in the dorsum of the left hand and ringer lactate in water infusion started at the rate of 20 drops/min, either of the three drugs (diazepam, lorazepam or

midazolam) was injected intramuscularly 45 minutes prior to induction, in the deltoid region in the mentioned dose. Various parameters like sedation score, anxiolysis, pulse rate, blood pressure and respiratory rate were recorded. Ranitidine 50 mg IV was given and each patient was asked to remember a colour and a number to be recalled after recovery from general anaesthesia as assessment of anterograde amnesia. After 45 min of premedication, the patient was shifted to operation theatre and injection tramadol HCL in a dose of 0.05 mg/kg body weight and inj. glycopyrrolate 0.02 mg given intravenously. Pre-oxygenation was done for 3 minutes with 100% oxygen using Magill's circuit. The patient was then immediately induced with inj. thiopentone sodium 2.5% injected slowly over 30 seconds titrating the dose with loss of eyelash reflex, followed by vecuronium bromide in a dose of 0.1 mg/kg body weight. Ventilation was assisted with 100% oxygen by face mask ventilation for three min and endotracheal intubation was performed within the shortest possible time. Pulse rate and blood pressure were recorded 2 minutes after intubation. Respiration was maintained by intermittent positive pressure ventilation with 66% nitrous oxide and 33% oxygen mixture through a closed circuit with soda lime absorber. IPPV was maintained with the help of repeat doses of vecuronium bromide. Injection ketorolac tromethamine 1 mg/kg body weight was given intramuscularly after 5 minutes of induction, ondansetron 4 mg IV given towards the end of the operation. Pulse rate and blood pressure were monitored constantly. At the end of surgery nitrous oxide was stopped, neuromuscular block reversed with neostigmine methyl sulphate 0.04 mg/kg and atropine sulphate 0.02 mg/kg body weight

given IV. Endo-tracheal extubation was done under direct vision following oro-pharyngeal toilet. Heart rate, blood pressure, respiratory rate, sedation score and anxiolysis were again recorded. Thereafter various parameters were recorded in the recovery room at 1 and 6 hours of reversal.

Data were exported to Microsoft excel spreadsheet (2007 version). Continuous variables are presented as mean with standard deviation after testing for normality. Ordinal data is presented as total number and percentage (%). They were examined with chi square test. A p value of <0.05 was considered as statistically significant.

RESULTS

Ninety patients were included in the study. Table 1 shows that the demographic data of the patients under study in the 3 groups were comparable in terms of age, sex, body weight and ASA gradings.

Almost identical types of surgeries were performed in each group showing that the 3 groups are comparable in terms of duration, nature and site of surgery.

All patients in the 3 study groups were awake and alert before premedication (Table 2). 6 hours after reversal it was observed that a majority of the patients in group III (23) were free from sedation whereas more than half of the patients in group I and group II were still under sedation. The observations show that the duration of action of diazepam and lorazepam are considerably longer than that of midazolam.

Table 1: Demographic data of the patients under study showing age, weight, sex, ASA gradings and types of surgery.

Variables	Group I (mean±SD)	Group II (mean±SD)	Group III (mean±SD)
Mean age (in years)	37.33±11.62	36.83±8.96	35.30±10.53
Mean weight (in Kg)	46.97±8.31	49.10±8.85	49.33±10.30
Male	6	4	9
Female	24	26	21
ASA grade I	17	20	18
ASA grade II	10	10	12
Types of surgery			
Appendicetomy	1	2	2
Cholecystectomy	19	18	19
Herniotomy/meshplasty	3	3	4
Subtotal thyroidectomy	0	1	1
Mastectomy (simple/radical)	4	4	3
Gastrojejunostomy	3	2	1

The quality of anxiolysis achieved after premedication at various time intervals in the three study groups are presented in Table 3. Fifteen minutes after premedication, 30% of patients in midazolam group showed good anxiolysis but none of the patients in diazepam group showed evidence of good anxiolysis (Table 3). After 45 minutes, maximum number of patients in group III

showed adequate reduction in apprehension followed by group II and group I. After reversal maximum numbers of patients in group III were free from anxiety. After 6 hours post operatively however, minimum number of patients in group III showed appreciable relief of anxiety. This was because of the short duration of action of midazolam.

Table 2: Showing assessment of sedation before and after premedication at various time intervals among three study groups.

Time interval	Group I: number of patients in each sedation score (%)					Group II: number of patients in each sedation score (%)					Group III: number of patients in each sedation score (%)							
	Sedation score					Sedation score					Sedation score							
	6	5	4	3	2	1	6	5	4	3	2	1	6	5	4	3	2	1
Before premedication	-	30 (100)	-	-	-	-	30 (100)	-	-	-	-	-	30 (100)	-	-	-	-	-
After premed-15 minutes	-	24 (80)	6 (20)	-	-	-	28 (93.3)	2 (6.7)	-	-	-	-	17 (56.7)	12 (40)	1 (3.3)	-	-	-
30 minutes	-	19 (63.3)	11 (36.7)	-	-	-	21 (70)	9 (30)	-	-	-	-	1 (3.3)	22 (73.3)	7 (23.3)	-	-	-
45 minutes	-	2 (6.7)	20 (66.7)	8 (26.7)	-	-	4 (13.3)	18 (60)	8 (26.7)	-	-	-	1 (3.3)	8 (26.7)	20 (66.7)	1 (3.3)	-	-
After reversal	-	6 (20)	18 (60)	6 (20)	-	-	-	18 (60)	1 (36.7)	1 (3.3)	-	-	1 (3.3)	23 (76.7)	5 (16.7)	1 (3.3)	-	-
After 1 hours	-	4 (13.3)	17 (56.7)	9 (30)	-	-	4 (13.3)	10 (33.3)	15 (50)	1 (3.3)	-	-	5 (16.7)	16 (53.3)	9 (30)	-	-	-
After 6 hours	-	11 (36.7)	10 (33.3)	9 (30)	-	-	10 (33.3)	16 (53.3)	4 (13.3)	-	-	-	23 (76.7)	5 (16.7)	2 (6.7)	-	-	-

Table 3: Showing assessment of anxiolysis after premedication at various time intervals in the three study groups.

Time interval	Group I: number of patients in each sedation score (%)				Group II: number of patients in each sedation score (%)				Group III: number of patients in each sedation score (%)			
	Ex	G	FR	P	Ex	G	FR	P	Ex	G	FR	P
15 minutes after pre-medication	-	-	6 (20)	24 (80)	-	-	5 (16.7)	25 (83.3)	-	9 (30)	19 (63.3)	2 (6.7)
30 minutes after pre-medication	-	-	22 (73.3)	8 (26.6)	-	-	6 (20)	24 (80)	4 (13.3)	20 (66.7)	6 (20)	-
45 minutes after pre-medication	-	11 (36.7)	17 (56.7)	2 (6.7)	3 (10)	11 (36.7)	16 (53.3)	-	14 (46.7)	14 (46.7)	2 (6.7)	-
After reversal	2 (6.7)	11 (36.7)	17 (56.7)	-	3 (10)	19 (63.3)	8 (26.6)	-	5 (16.7)	18 (60)	7 (23.3)	-
After 1 hour (Post op)	2 (6.7)	13 (43.3)	15 (50)	-	5 (16.6)	16 (53.3)	9 (30)	-	1 (3.3)	18 (60)	11 (36.7)	-
After 6 hour (Post op)	2 (6.7)	14 (46.7)	14 (46.7)	-	3 (10)	16 (53.3)	11 (36.7)	-	-	8 (26.7)	22 (73.3)	-
After 12 hour (Post op)	3 (10)	15 (50)	12 (40)	-	-	14 (46.7)	16 (53.3)	-	-	-	27 (90)	3 (10)
After 24 hour (Post op)	-	8 (26.7)	22 (73.3)	-	-	2 (6.7)	28 (93.3)	-	-	-	27 (90)	3 (10)

Ex-excellent, G-good, FR-fair, P-poor.

The mean pulse rate before premedication in the three study groups were not significantly different ($p>0.05$). After premedication, a significant change in mean pulse

rate was observed after 15 minutes in midazolam group, after 30 minutes in diazepam group and after 45 minutes in lorazepam group (Figure 1).

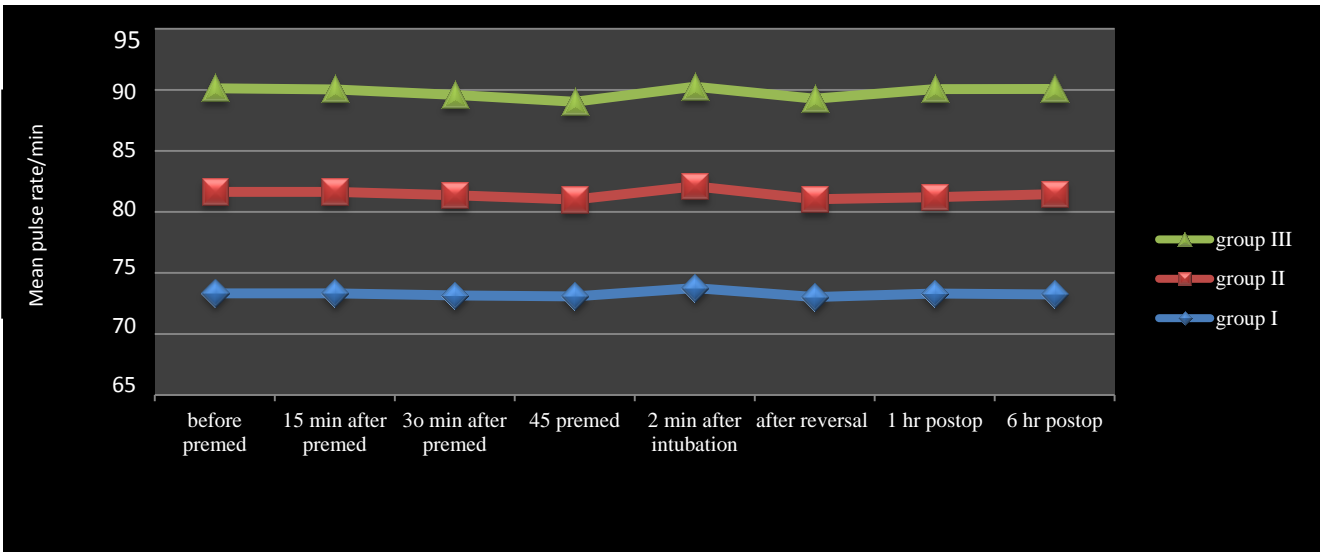


Figure 1: Values of mean pulse rate at various time intervals before and after premedication.

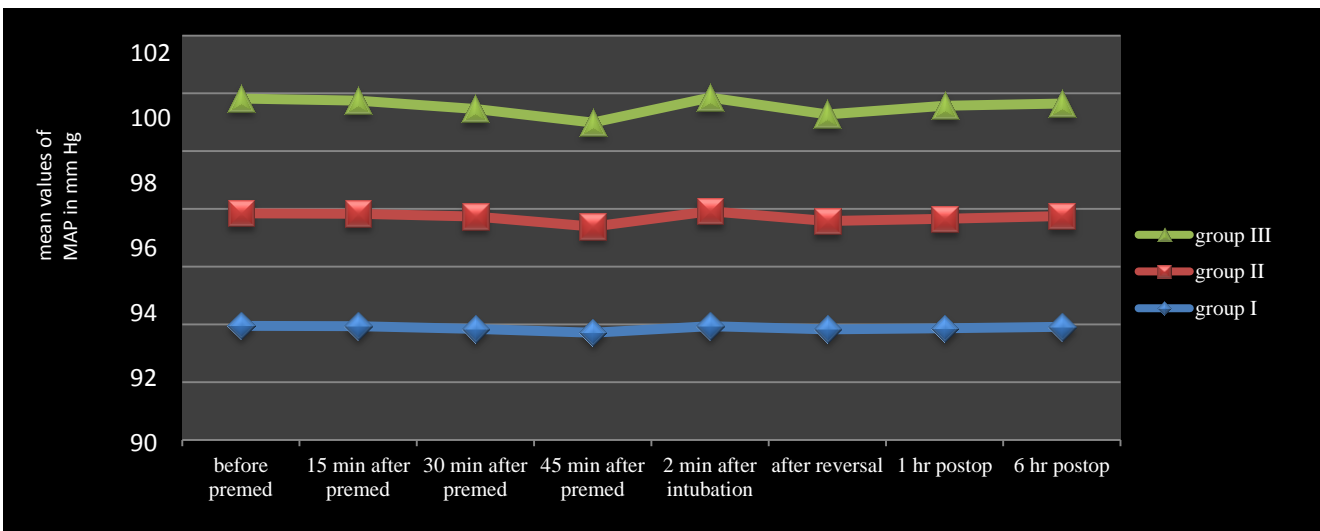


Figure 2: Values of mean arterial pressure at various time intervals before and after premedication.

The mean arterial pressure before premedication in the three study groups were not significantly different ($p>0.05$) (Figure 2). After premedication, a significant fall in mean arterial pressure was observed 15 minutes in midazolam group, after 30 minutes in diazepam group and after 45 minutes in lorazepam group (Figure 2).

Mean values of respiratory rate before and after premedication have been compared in the 3 study groups using the paired ‘t’ test. It was found that the mean values were not significantly different ($p>0.05$) prior to premedication. The Figure 3 shows that all the 3 groups show the significant but transient change in respiratory

rate and there was a stable and adequate respiratory rate in the postoperative period.

Anterograde amnesia after premedication was evaluated and compared among the three study groups using “chi square test”. Three hours after recovery, amnesia was recorded in 83.33% of patients in midazolam group, 76.67% of patients in lorazepam group and only 46.67% of patients in diazepam group which clearly shows that both lorazepam and midazolam provide considerably better amnesia than diazepam (Figure 4). P value between group II and group III was insignificant ($p>0.05$).

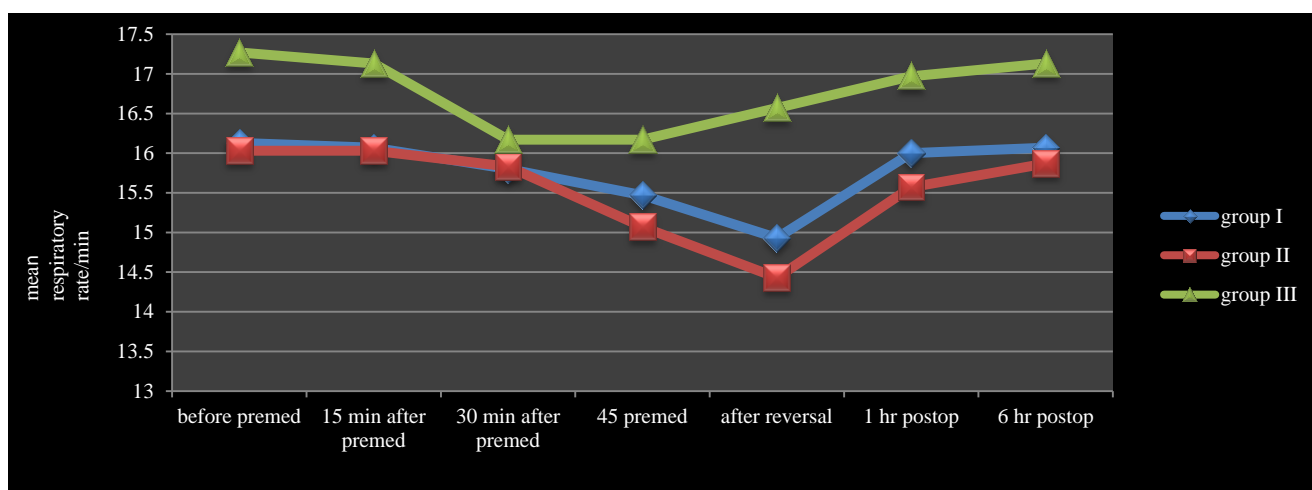


Figure 3: Values of respiratory rate before and after premedication at various time intervals.

Side effects and complications were also observed and recorded. Two patients (one each in lorazepam and midazolam groups) showed hiccough during induction. Two of the patients (one each in diazepam and lorazepam groups) showed delayed recovery. Two of the patients (one each in diazepam and lorazepam) had prolonged sedation. One patient in midazolam group had respiratory depression which was managed.

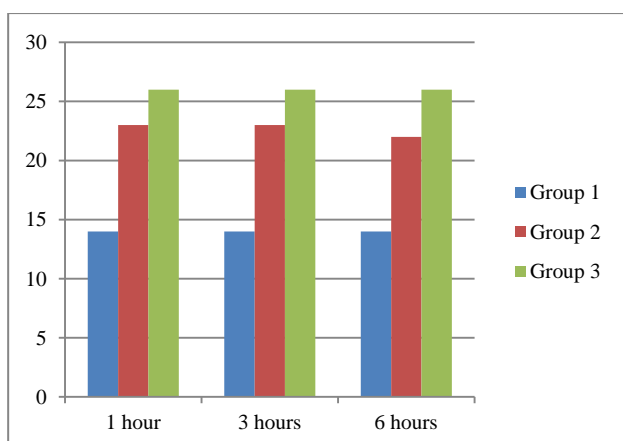


Figure 4: Assessment of amnesia in the three study groups.

DISCUSSION

This prospective randomized study was carried out with a view to evaluate the anxiolytic, sedative and amnesic properties of three benzodiazepines namely diazepam, lorazepam and midazolam as premedicant before general anaesthesia.

The only other study than ours which has conducted study on all the three drugs was that of Segan et al in 1992.⁷ Their route of administration is the same as ours. The dose of diazepam is similar in both but the dose of midazolam is slightly less in comparison to them.

Numbers of female patients are more than male patients in the present study, may be due to the fact that most of the patients were scheduled for cholecystectomy and incidence of gallstones is more prevalent in females in the north eastern part of India.

The present study showed that midazolam provided maximum relief of apprehension followed by lorazepam and diazepam which is very much similar with that of the findings by other authors.⁷⁻⁹

In the present study, sedation has been evaluated on the basis of scores described by Vinik et al.⁵ Before the procedure, anxiety scores of the patients in all the groups were similar (51 mm on the 100 mm analogue scale). During the procedure however, the patients sedated with midazolam were considerably less anxious than those receiving lorazepam or diazepam. Maximum degree of sedation was achieved with midazolam followed by lorazepam and diazepam. Duration of sedation was however maximum with diazepam and minimum with midazolam. Our results tally with that of other previous works that concluded that midazolam is superior to diazepam in onset and degree of sedation.⁹⁻¹¹

The study by Segan et al has found that midazolam is the best sedative among the three drugs compared, followed by lorazepam and diazepam, which is exactly similar to what we have found in the present study.⁷

The dose of thiopentone used as inducing agent was also lowered significantly in case of midazolam ($p < 0.05$) which conforms with the a previous study that observed that thiopentone dose requirement for induction of anaesthesia was reduced by 50% with prior use of Midazolam.¹²

Before premedication the mean values of pulse rate, blood pressure and respiratory rate were not significantly different among the three study groups ($p > 0.05$). Maximum changes (fall) in pulse rate, blood pressure,

respiratory rate were observed with midazolam followed by lorazepam and diazepam which facilitated haemodynamic stability during induction.

Anterograde amnesic effect and loss of recall were found to be maximum with midazolam. This finding conforms with that by many previous authors.^{10,13}

In our study, one patient in midazolam group showed respiratory depression where intervention was required. Delayed recovery and prolonged sedation in altogether four patients receiving lorazepam and diazepam requiring close monitoring, but the effects were self-limiting. Respiratory depression was observed in 3 patients (1 midazolam, 2 diazepam) in a study of 85 patients by Magni et al.¹⁴

In another study prolonged sedation was observed in the sublingual group compared to intramuscular group of lorazepam.¹⁵

Midazolam was found to be preferable to diazepam and lorazepam because shorter duration of action provided lesser chances of delayed recovery or prolonged sedation.

CONCLUSION

We concluded that all the three drugs evaluated in this study, namely midazolam, diazepam and lorazepam are useful as intramuscular premedication before general anaesthesia but diazepam and lorazepam are suitable in cases where surgery is of longer duration or where post-operative sedation is required. Midazolam, however offers the maximum advantage in allaying anxiety and providing excellent sedation and amnesia during general anaesthesia and proves to be the most suitable premedicant before general anaesthesia.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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