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Original Article

Anaesthesia Section

Effect of Different Dosages of Intravenous Midazolam Premedication on Patients Undergoing Head and Neck Surgeries- A Double Blinded Randomized Controlled Study

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ABSTRACT

Introduction: Benzodiazepines primarily acts on the central nervous system. Most patients are extremely anxious in the pre-operative period. Excessive anxiety adversely influences anaesthetic induction and often leads to functional impairment and poor recovery after surgery.

Aim: To determine whether amnesia, anxiety, sedation and cardio respiratory symptoms are affected while administering two different doses of intravenous midazolam (0.02 mg/kg & 0.06 mg/kg).

Materials and Methods: Two forty patients posted for head and neck surgeries were involved in this double blinded prospective randomised controlled trial. The patients were randomized into two main groups, Group 1 receiving 0.02 mg/kg and Group 2 receiving 0.06 mg/kg midazolam intravenously as premedication. Visual recognition and recall were tested using eight laminated A4 size posters pre-operatively and four further images were shown at the postoperative interview. Anxiety was evaluated by a Visual Analogue Scale (VAS) and sedation depth was determined by the Observer's Assessment of Alertness/Sedation Scale (OAAS) scale. Vital signs including heart rate, respiratory rate, mean blood pressure and arterial oxygen saturation (SpO_2) were monitored. Statistical analysis was done using paired Student's t-test and Chi-square test.

Results: VAS scores were lower in Group 2 (0.06 mg/kg) than in Group 1 (0.02 mg/kg) at T_{15} (15 minutes after the injection of midazolam). Comparison of OAAS scores among Group 1 and Group 2 showed that more patients in Group 1 were alert at T15 compared to Group 2. Recall of events was significantly lower in Group 2 compared to Group 1. There was no significant statistical variation in haemodynamic parameters between the groups except for decreased diastolic blood pressure and room air saturation in Group 2.

Conclusion: A higher dosage of midazolam improves the quality of anxiolysis and sedation with lesser rates of intraoperative recall and maintains haemodynamic stability.

Keywords: Benzodiazepines, Observer's assessment of alertness/sedation scale, Visual analogue scale

INTRODUCTION

Benzodiazepines are a group of psychoactive drugs having prominent effects like sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia and anticonvulsant activity. However, at preanaesthetic doses the drug produces amnesia for subsequent events which may create an illusion of previous anaesthesia [1].

Benzodiazepines produce their effects by facilitating the actions of Gamma Amino Butyric Acid (GABA), the principal inhibitory transmitter of the CNS [2].

Midazolam is a sedative drug with amnesic properties. Previous studies have found that anterograde but not retrograde amnesia can be demonstrated with midazolam [3].

However, the time period in which memory was studied was typically one hour or more prior to drug administration. This time frame does not adequately address the period of most clinical relevance to anaesthesiologists. Studies have shown that drugs like propofol at higher dosages can induce retrograde amnesia like midazolam [4].

There are not much studies involving onset, dose response and amnestic properties of midazolam at the usual clinically used dose range of 1-5 mg [5].

Hence, this study was undertaken to assess the effects of premedication with midazolam one hour prior to surgery which is of importance to anaesthesiologists.

Different dosages for intravenous midazolam premedication are known [6]. The recommended premedication dosage is 1-1.5 mg (0.02 mg/kg) and total dosage should not exceed 3.5 mg or 0.07 mg/kg in the elderly [7]. This was the basis for the selection of the two different dosages for our study.

MATERIALS AND METHODS

After obtaining Ethical Committee approval and informed consent from all patients, this double blinded randomised clinical study was conducted on 240 patients scheduled to undergo elective head and neck surgeries. Patients were stratified into two dose groups, Group 1 received 0.02 mg/kg of intravenous midazolam (Mezolam 1 mg/ml, Neon Pharmaceuticals) and Group 2 receiving 0.06 mg/kg of midazolam. Randomization was achieved by the computer generated random numbers held in sealed envelope by an individual not involved with the study. Each group had 120 subjects.

The inclusion criteria included American Society of Anaesthesiologist's (ASA) physical status 1 or 2, age above 20 years, weight 50-100 kilograms, all elective head and neck surgeries undergoing general anaesthesia.

Exclusion criteria were ASA physical class of 3 or higher, pregnant patients, patients with psychiatric disorders and those taking antipsychotics, sedative or tranquilizer in the last 24 hours, known or suspected memory impairment, neurosurgical procedures,

visual or hearing impairment, chronic use of benzodiazepines, use of β-blockers or calcium channel blockers and hypersensitivity to midazolam.

Patients were brought to the preoperative holding area adjacent to the operating room. An intravenous access was secured and monitors were attached and vitals were recorded 15 minutes prior to the administration of midazolam.

Drug syringes were prepared by an anaesthesiologist who was not involved in the study. Midazolam (0.02 or 0.06 mg/kg) was diluted in normal saline to a total volume of 6 ml.

The patients were premedicated one hour before surgery with either of the doses by an anaesthesiologist blinded to the drug injected. Midazolam was administered intravenously over 15-20 seconds. An anaesthesiologist blinded to the patient allocation and study drugs did the clinical assessments. The primary outcomes measured were Heart Rate (HR) variation, Blood Pressure (BP) variation, Respiratory Rate (RR) variation, oxygen saturation and assessment of the patient's level of anxiety and sedation.

Anxiety was evaluated by a VAS. The VAS consisted of a 100 mm horizontal line with "no anxiety at all" as score 0 and "extreme anxiety" as score 100 on the other end. Patients were asked to indicate their levels of anxiety 15 minute before (T_{-15}) and 15 minute after midazolam administration (T_{+15}).

Depth of sedation was determined by the OAAS [8]. The OAAS measured sedation on a 1 (does not respond to mild prodding or shaking) to 5 (responds readily to name spoken in normal tone) scale. Patients with OAAS scores 3, 4 and 5 could respond to verbal commands and were classified as conscious. Those who did not respond (scores of 1 and 2) were considered to be unresponsive or unconscious.

The acceptable level of sedation depended on the performed procedure and psychological and physiological status of the patient. For the purpose of this study the acceptable level was a score ≥3.

The secondary outcome measured includes recall of pre-operative and intra operative events.

Visual recognition and recall were tested using eight laminated A4 size posters. There were four images designated as pre-operative images (PRE1–PRE4) each with a unique easily recognizable simple image, PRE1 (shoe); PRE2 (sea); PRE3 (glass); PRE4 (book). They were shown to each patient at T_{-4} min (Four minutes prior to showing the fourth picture) (PRE1), T_{-3} min (PRE2), T_{-2} min (PRE3) and T_{-1} min (PRE4).

Patients were asked to identify the posters. Along with the above posters, four more posters were shown in the post operative interview as controls. The sequence of showing posters pre-operatively was PRE1–4; and postoperatively was PRE1, PRE2, POST8, PRE3, PRE4, POST5, POST6, POST7.

Recall of the intraoperative events was also assessed at specific time intervals. T_{-2i} min: patient moved to the operating table, T_{-1i} min: patient requested to put out their tongue, T_{0i}: pre oxygenation started via mask (until induction), T_{+4i} min: patient asked to shut his/her eyes and then open them, T_{+8i} min: patient was told that he will get sedated with the injection of the drug.

At the postoperative period, patients were asked about recall of the above events. An additional fictitious finger-prick test was done as a control to identify any false recollections.

Vital signs including heart rate, respiratory rate, mean blood pressure and arterial oxygen saturation (SpO_2) were continuously monitored. Values 15 minutes prior (T_{-15}) and 15 minutes after midazolam administration (T_{+15}) was noted down. Complications after the midazolam administration including apneas (intermittent respiratory pause >10s), cardiac arrhythmias, hypotension (fall >20%), and subjective complaints of discomfort by the patients were noted and recorded. A subject was judged to require supplemental oxygen at 5 L/min if saturation was less than 85%. After completion of these observations, patients were shifted to the operating theatre.

STATISTICAL ANALYSIS

To determine sample size, Cohen's [9] tables were used. According to these tables, a medium-sized effect for analysis of variance (ANOVA) was 0.25. A sample size calculation of two groups was needed. A total sample size of 210 was needed. Therefore, the sample size of 240 in this study was appropriate. Patient characteristic data were compared using independent sample t-test. Physiological data were averaged and compared by ANOVA test. Correlation coefficient and regression analysis were used in outcomes. Paired t-test and Mann-Whitney U test were used for statistical analysis. The p-value>0.05 is considered not significant, p-value≤0.05 as significant and p-value≤0.001 as highly significant.

RESULTS

Both groups were equally matched for gender [Table/Fig-1].

Comparison of VAS for anxiety level among Group 1 and Group 2 showed no significant statistical difference (after applying paired t-test) existed between the scores at T_{-15} (p-value=0.078) whereas highly significant difference existed between the scores of two groups at T_{+15} (p-value=0.001) [Table/Fig-2]. At higher dose of midazolam there was considerable decrease in anxiety levels of patients.

Comparison of OAAS scores among Group 1 and Group 2 using the Mann-Whitney U test showed that no significant statistical difference existed between the scores at T_{-15} (p-value=0.09) whereas highly significant difference existed between the scores of two groups at T_{+15} (p-value=0.001) [Table/Fig-2].

The depth of sedation was more with higher dose of midazolam than with lower dose. At T_{+15}, the OAAS level of 2 was 0 (0%) in Group 1 and in Group 2 were 7 (5.8%). OAAS level of 3 was 41 (34.2%) in Group 1 and in Group 2 was 6 (50.8%). OAAS level of 4

Variables			Group		Total
			Group 1 (0.02 mg)	Group 2 (0.06 mg)	
Gender	Male	Count %	68 56.7%	59 49.2%	127 52.9%
	Female	Count %	52 43.3%	61 50.8%	113 47.1%
Total	Count %		120 100%	120 100%	240 100%

[Table/Fig-1]: Gender distribution.
χ^2=1.355, p-value=0.244 (not significant).

Parameters	T-15 (mean±SD)		p-value	T+15 (mean±SD)		p-value
	Group 1 (0.02 mg)	Group 2 (0.06 mg)		Group 1 (0.02 mg)	Group 2 (0.06 mg)	
VAS†	42.93± 21.21	48.14± 20.06	0.078***	24± 23.5	9.63± 14.68	0.001 *
OASS‡‡	4.94± 0.23	4.98± 0.12	0.09***	4.05± 0.86	3.48± 0.76	0.001*
HR‡	83.19± 13.75	82.56± 13.05	0.718***	70.29± 14.55	69.47± 13.74	0.655***
SBP‖	138.24± 16.7	138.65± 16.4	0.846***	120.98± 16.7	117.9± 15.8	0.147***
DBP§	84.1± 12.53	82.63± 12.8	0.37***	70.8± 11.58	67.78± 11.9	0.049**
$Spo_2$$	99.95± 0.23	99.99± 0.09	0.155***	99.8± 0.8	99.95± 1.46	0.044**
RR††	14.47± 2.1	14.11± 2.38	0.218***	13.1± 1.55	12.85± 1.9	0.267***

[Table/Fig-2]: Parameters.
† Visual analogue scale, ‡‡ Observer's assessment of alertness/sedation scale,‡ Heart rate, ‖ Systolic blood pressure, § Diastolic blood pressure, * Oxygen saturation, ††Respiratory rate,
* Highly significant (p-value≤0.001), ** Significant (p-value≤0.05), ***Not significant (p-value>0.05).

Parameters			Group		Total
			Group 1 (0.02 mg)	Group 2 (0.06 mg)	
Preoperative Recall	<50%	Count %	27 22.5%	72 60%	99 41.3%
	>50%	Count %	93 77.5%	48 40%	141 58.8%
Total	Count %		120 100%	120 100%	240 100%

[Table/Fig-3]: Preoperative recall of pictures.
χ^2=34.816, p-value≤0.001 (highly significant)
Chi-square test was applied and statistically significant difference existed between the two groups (p-value≤0.001) for preoperative recall. Preoperative recall was more in patients in the 0.02 mg/kg group, while recall was less in the 0.06 mg/kg group.

Parameters			Group		Total
			Group 1 (0.02 mg)	Group 2 (0.06 mg)	
Intraoperative Recall	<50%	Count %	55 45.8%	83 69.2%	138 57.5%
	>50%	Count %	65 54.2%	37 30.8%	102 42.5%
Total	Count %		120 100%	120 100%	240 100%

[Table/Fig-4]: Intraoperative recall.
χ^2=13.367, p-value≤0.001 (highly significant)
Chi-square test was applied and statistically significant difference existed between the two groups (p-value≤0.001). Intraoperative recall was more in patients in the 0.02 mg/kg group, while recall was less in the 0.06 mg/kg group.

was 31 (25.8%) in Group 1 and in Group 2 was 39 (32.5%). OAAS level of 5 was 48 (40%) in Group 1 and in Group 2 was 13(10.8%).

Comparison of heart rate, systolic blood pressure and respiratory rate among Group 1 and Group 2 [Table/Fig-2], using paired Student's t-test, showed that neither any significant statistical difference existed between the scores at T_{-15} nor any statistically difference existed between the scores of two groups at T_{+15}.

Comparison of diastolic blood pressure among Group 1 and Group 2 [Table/Fig-2]. Statistical analysis by applying the paired Student's t-test between the two groups showed that no significant statistical difference existed between the scores at T_{-15} with a p-value of 0.37 whereas significant statistical difference existed between the scores of two groups at T_{+15} with a p-value of 0.049.

Comparison of oxygen saturation in room air among Group 1 and Group 2 [Table/Fig-2]. Statistical analysis by applying the paired Student's t-test between the two groups showed that no significant statistical difference existed between the scores at T_{-15} with a p-value of 0.155 whereas significant statistical difference existed between the scores of two groups at T_{+15} with a p-value of 0.044.

Comparison of preoperative recall of pictures among Group 1 and Group 2. Statistical analysis by applying the Chi-square test between the two groups it was found that highly significant statistical difference existed between the two groups with a p-value≤0.001 [Table/Fig-3].

Group 1 (0.02 mg/kg): Recall of less than 50% of the events was achieved by 27 patients (22.5%) and of more than 50% was achieved by 93 patients (77.5%)

Group 2 (0.06 mg/kg): Recall of less than 50% of the events was achieved by 72 patients (60%) and more than 50% was achieved by 48 patients (40%).

Preoperative recall of the events was more in patients in the 0.02 mg/kg group, while recall was less in the 0.06 mg/kg group.

Comparison of recall of intraoperative events by applying the Chi-square test between the two groups showed that highly significant statistical difference existed between the two groups with a p-value≤0.001 [Table/Fig-4].

Group 1 (0.02 mg/kg) recall of less than 50% was achieved by 55 patients (45.8%) and more than 50% of events were achieved by 65 patients (54.2%).

Group 2 (0.06 mg/kg) recall of less than 50% of the events were achieved by 83 patients (69.2%) and more than 50% was achieved by 37 patients (30.8%).

Intraoperative recall was more in patients in the 0.02 mg/kg group, while recall was less in the 0.06 mg/kg group.

DISCUSSION

In our study it was demonstrated that clinically relevant difference can be seen with the usage of higher doses of midazolam premedication. Higher doses reduced the anxiety levels and increased sedation level. The safety of higher doses of midazolam (0.06 mg/kg) was found to be acceptable inspite of variation in saturation and diastolic blood pressure. To our knowledge, this is the first study which systematically evaluated the effects of two doses of midazolam on recall of events. The preoperative and intraoperative recall of events was considerably less with higher doses of midazolam.

Sun GC et al., studied the effects of two different doses of midazolam premedication on age and gender. In this study the dosage of intravenous midazolam chosen were 0.02 and 0.06 mg/kg midazolam. They concluded that midazolam is effective for producing sedation and anxiolysis at a dose of 0.02 mg/kg, with minimal effects on cardiorespiration and oxygen saturation to patients [10]. It was found that a higher level of preoperative anxiety was observed in women than in men, and in young than in older patients. A higher dose of midazolam produced significant haemodynamic changes compared to lower doses which were comparable to our findings. Also, the depth of sedation was more with higher doses which was similar to our findings.

Nishayama T conducted a study on 180 patients aged 20–50 years scheduled for spinal anaesthesia. He premedicated patients with 0.06 mg/kg midazolam and 0.01 mg/kg atropine intramuscularly before giving spinal anaesthesia. After subarachnoid block different dosages of midazolam were given intravenously ranging from 0, 0.02, 0.03, 0.04 to 0.05 mg/kg. Patients were assessed for eye lash reflex, verbal response, involuntary movements and memory. The values were more in the groups receiving higher dosages of midazolam. These findings were comparable with our study where OASS and VAS were less in Group 2 compared to Group 1 [11].

In another study, 40 children aged 1-5 years were enrolled and randomly assigned into two groups and receive oral preparation of midazolam with doses of 0.5 mg/kg (Group I) and 0.75 mg/kg (Group II), 30 minutes before separation from parents. They were assessed for patient's acceptance of the medication, reaction to separation from the parents, sedation scores and recovery conditions. The results showed that separation anxiety was less in Group II compared to Group I. The sedation scores were higher in Group II than Group I. The time to recover from anaesthesia was not different in the two groups [12]. These results were comparable to our findings even though the route of premedication was oral compared to intravenous route which was done in our study.

In a study comparing 125 patients who were randomized into three groups: Group I (control group), Group II (dexmedetomidine 1 µg/kg) and Group III was the midazolam group which was further divided into three subgroups, Group IIIA (0.02 mg/kg), Group IIIB (0.04 mg/kg), and Group IIIC (0.06 mg/kg). Ramsay sedation scores and VAS scores were lower for the group that received higher doses of midazolam which were similar to our findings [13].

In a placebo controlled trial comparing the effects of 0.025 mg/kg midazolam with saline in patients undergoing cesarean section, it was found that anxiety scores were lower in mothers receiving intravenous midazolam.These findings were similar to our findings where midazolam premedication considerably reduced the anxiety scores [14].

Thus, midazolam has been shown to be effective when used for preoperative sedation. Midazolam sedation is known to produce

few deleterious effects such as respiratory depression, hypoxaemia, and apnoea, which are associated with higher doses. Excessive sedation is often accompanied by low oxygen saturation during midazolam administration [15].

LIMITATION

A limitation of the study is that we could have stratified the study groups according to age and gender as these parameters are likely to influence the outcome of the study [10]. Studies have shown that endogenous hormones have influence on the effects of sedative drugs [16].

CONCLUSION

A higher dosage of midazolam (0.06 mg/kg) produces better quality of anxiolysis and sedation with lesser rates of intraoperative recall without significantly affecting the heart rate, respiratory rate and systolic blood pressure as compared to a lower dose (0.02 mg/kg). However, higher dose (0.06 mg/kg) causes a significant fall in diastolic blood pressure and oxygen saturation in room air.

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