RESEARCH ARTICLE

Comparison of Effectiveness and Side Effects of Diazepam versus Midazolam Administration for Conscious Sedation in Patients Who Underwent Cataract Surgery

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Background: The purpose of this study was to compare the effectiveness and side effects of diazepam and midazolam administration for conscious sedation in subjects who undergoing cataract surgery.
Methods: A total of 79 patients undergoing cataract surgery under topical anesthesia with conscious sedation were prospectively reviewed. Our subjects were randomly divided to two groups. The first group comprised of 38 cases receiving 0.05 mg/kg diazepam slow intravenously (diazepam group) and the second group comprised of 41 cases receiving 0.01 mg/kg midazolam intravenously (midazolam group). Intraoperative variables such as systolic and diastolic arterial pressure, heart rate, respiratory rate and blood oxygen saturation were recorded immediately before sedation, 5, 10 and 15 minutes after diazepam or midazolam administration. All patients were contacted 24 hours after the operation for any early postoperative complications.
Results: The variability of systolic and diastolic blood pressure at 5, 10 and 15 minutes after sedation were statistically significantly higher in midazolam group compared to diazepam group. Six patients developed episodes of apnea during operation, two patients in diazepam and four patients in midazolam group. The surgeons' satisfaction was more in diazepam group but not statistically significant. Need for additional dose of benzodiazepine was more in the midazolam group. Drowsiness and functional impairment during 24 hours after surgery were not significantly different between the two groups.
Conclusion: Diazepam produces better perioperative hemodynamic profile, level of sedation and surgeon's satisfaction and less occurrence of apnea compared to midazolam group in patients who underwent cataract surgery.
Keywords: Diazepam; Midazolam; Cataract surgery; Conscious sedation; Topical anesthesia

Cataract surgery is usually carried out using topical anesthesia under conscious sedation in many centers. Topical anesthesia accompanying conscious sedation prefer to regional or general anesthesia especially in elderly patients [1]. Length of hospital stay and postoperative events such as nausea and vomiting are reduced with conscious sedation compared to general anesthesia in patients undergoing cataract surgery [2]. This procedure is usually performed on octogenarian subjects and many of these patients have systemic illnesses [3]. Half of these subjects have hypertension [4]. Currently anesthesiologists frequently administer a combination of an opioid such as fentanyl and one benzodiazepine such as midazolam during cataract surgery. Because of reduced systemic functional reserve in elderly patients, drug interaction and synergic effect of opioid and benzodiazepine may exhibit hemodynamic disturbance, respiratory depression and delayed recovery after conscious sedation [5]. Midazolam introduced in the mid 1980s gained popularity because of excellent anterograde amnesia, shorter elimination half-life and faster recovery and reduced risk of venous phlebitis [6]. However, shortly after midazolam introduction, its safety in conscious sedation especially in elderly subjects was seriously questioned because of relative overdose [7]. Both diazepam and midazolam led to respiratory depression especially when combined with an opioid [8]. However, it was shown that an equipotent dose of these agents during conscious sedation does not cause equivalent respiratory depression [9]. The purpose of this study was to compare the effectiveness and side effects of diazepam and midazolam in combination with fentanyl in subjects who undergoing cataract surgery with conscious sedation.

Methods

A total of 79 patients aged 42-86 years undergoing cataract surgery under topical anesthesia with conscious sedation in Farabi eye hospital between October 2018 and December 2018 were prospectively reviewed. This study was approved by the hospital ethics committee and informed consents were obtained from all of our patients. Patients with significant

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heart, renal, liver disease, allergy to opioid and benzodiazepine, subjects receiving psychotropic agents and those with impaired mental function were excluded from this study. Demographic variables and surgical characteristics of our patients were recorded. All patients received no premedication. Patients were randomized to two groups by use of computer-generated randomization table. All patients were monitored with automatic blood pressure cuff, electrocardiogram and pulse oximeter during operation. Supplemental oxygen 5 liter/minute by face mask was administered during the procedure. Our subjects received 1µg/Kg fentanyl intravenously and were randomly divided to two groups. The first group comprised of 38 cases receiving 0.05 mg/kg diazepam slow intravenously (diazepam group) and the second group comprised of 41 cases receiving 0.01 mg/kg midazolam intravenously (midazolam group) over three minutes prior to topical anesthesia. The sedative end-point in our subjects was defined when the patients were calm, relaxed and satisfied during surgical proceeding. The investigator and patients were unaware of which benzodiazepine was administered in patients. The syringes of benzodiazepine were prepared by a nurse of anesthesia not involved in this study. In patients who needed additional dose of benzodiazepine, the anesthesiologist administered 25 percent of the initial dose to maintain the desired level of sedation during operation. Patients received other medications such as antihypertensive agents till morning of the procedure. All patients evaluated before operation based on cognitive skills and excluded subjects with dementia. The state of consciousness was scored by use of the standard observer's assessment of alertness and sedation (OAAS) scale [10]. This scale ranges from 1 (unresponsive) to 5 (fully awake) and we considered target level 3 for all subjects in our study. Intraoperative variables such as systolic and diastolic arterial pressure, heart rate, respiratory rate and blood oxygen saturation were recorded immediately before sedation, 5, 10 and 15 minutes after diazepam or midazolam administration and in the recovery unit in both groups. Blood pressure was measured in the supine position intraoperatively and in the recovery room. All patients underwent cataract surgery with phacoemulsification technique under topical anesthesia and conscious sedation. In this study we considered a patient as apnoeic if no breathing was observed for a period longer than 15 second. If saturation of oxygen decreased to less than 85% by pulse oximetry, the anesthesiologist managed hypoxemia by verbal and tactile stimulation and airway maneuvers such as administration of supplemental oxygen and chin lift or jaw thrust. Patients were discharged from recovery unit if fully awake, hemodynamically stable and had clinically adequate ventilation and oxygenation. All patients were contacted 24 hours after the operation and complaints of postoperative complications such as drowsiness, physical and cognitive impairment were recorded. Data are presented as means± SEM. Subjective measures were evaluated by chi-square analysis. Blood pressure and oxygen saturation were analyzed with repeated measures analysis of variance. P< 0.05 was considered statistically significant.

Results

The mean age was 67.5±10 and 66.9±12 years in diazepam and midazolam groups respectively. Both groups as regards gender, weight and ASA class were not statistically significantly different (Table 1). The systolic and diastolic blood pressure, heart rate and saturation of oxygen level measured preoperatively were not statistically significantly different between two groups. The prevalence of co-exiting disease between two groups was not statistically significant (Table 1). The variability of systolic and diastolic blood pressure at 5, 10 and 15 minutes after sedation were statistically significantly higher in midazolam group compared to diazepam group (Figure 1-2). Six patients developed episodes of apnea during operation, two patients in diazepam and four patients in midazolam group. The level of sedation of patients during operation was less in diazepam group compared to another group. Moreover, the surgeon's satisfaction five minutes after diazepam or midazolam administration was more in diazepam group but not statistically significant. Need for additional dose of benzodiazepine was more in the midazolam group. The level of sedation 30 minutes after benzodiazepine administration and in the recovery room was not statistically different between two groups. Nausea and vomiting were not statistically significant between two groups. Drowsiness and functional impairment during 24 hours after surgery were not significantly different between the two groups. Mild tenderness at the injection site at 24 hours postoperative assessment was identified in one subject in diazepam group as against two subjects in the midazolam group (Table 2).

Figure 1- Comparison of systolic blood pressure in diazepam and midazolam groups

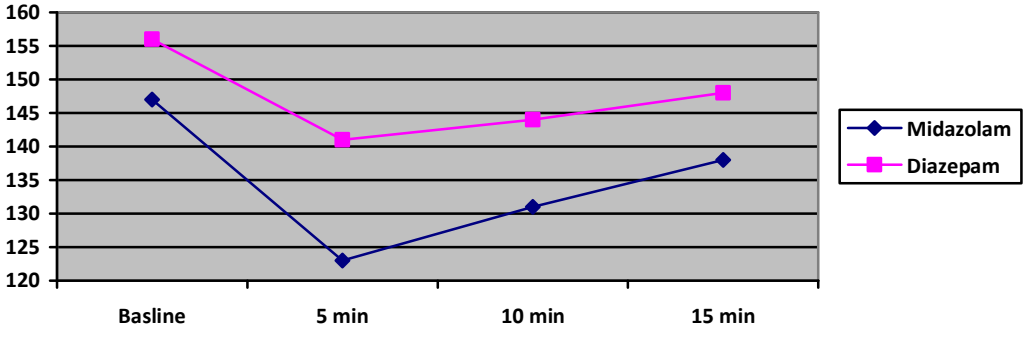

Figure 2- Comparison of diastolic blood pressure in diazepam and midazolam groups

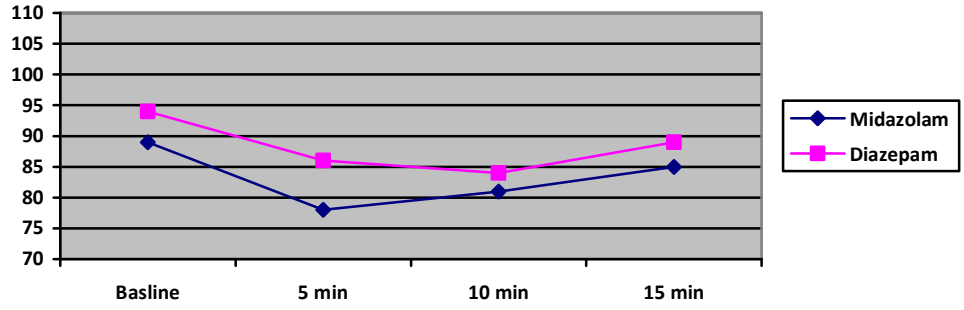

Table 1- Comparison of preoperative characteristics between diazepam and midazolam groups.

Variables	Diazepam group	Midazolam group	P value
Age (yrs)	67.5±10	66.9±12	0.81
Sex (male)	16 (42.1%)	17 (41.5%)	0.95
Weight (Kg)	76.2±14	78.4±10	0.42
ASA class	2.4±0.8	2.5±0.6	0.32
Diabetes	9 (23.7%)	4 (9.8%)	0.13
Hypertension	17 (44.7%)	12 (29.3%)	0.15
Systolic BP before sedation (mmHg)	156±25	147±24	0.10
Diastolic BP before sedation (mmHg)	94±14	89±13	0.15
Heart rate	68±10	69±12	0.42
Oxygen saturation (%)	97±1.4	98±1.2	0.89

Table 2- Comparison of intraoperative and postoperative characteristics between diazepam and midazolam groups

Variables	Diazepam group	Midazolam group	P value
Systolic BP 5 min after sedation	141±19	123±21	<0.001
Diastolic BP 5 min after sedation	86±12	78±15	0.01
Systolic BP 10 min after sedation	144±18	131±19	0.003
Diastolic BP 10 min after sedation	84±15	81±12	0.35
Systolic BP 15 min after sedation	148±16	138±18	0.04
Diastolic BP 15 min after sedation	89±10	85±12	0.45
Episode of apnea	2 (5.2%)	4 (9.7%)	0.64
Level of sedation (OAAS scale)	3.8±10	3.2±0.8	0.08
Need to additional dose of benzodiazepine	10 (26.3%)	18 (43.9%)	0.13
Surgeon satisfy	34 (89.4%)	28 (68.2%)	0.15
Nausea and vomiting	5 (13.2%)	3 (7.3%)	0.39
Postoperative functional impairment	0 (0%)	2 (4.9%)	0.59
Tenderness at the injection site	1 (2.6%)	2 (4.9%)	0.59

Discussion

Cataract surgery is a worldwide surgical procedure that is commonly performed and most of the patients are elderly. Performing cataract surgery with topical anesthesia alone causes pain and discomfort in more than 30% subjects [11]. We can decrease pain and discomfort of patients with administration of sedation agents [12]. Sedation agents were used in order to provide analgesia, anxiolytic effects, patients comfort and hemodynamic stability. The ideal agents for cataract surgery usually performed as outpatient procedure should have a rapid onset of action, short time duration of action and provide optimal relaxation. Diazepam

has a sedative, anxiolytic and anticonvulsant effects and acts through GABA-A receptors that induces central nervous system depression [13]. Early in the clinical practice of midazolam administration it was believed that this agent had effect twice as potent as diazepam [14]. Based on this finding midazolam distributed only as 5 mg/mL in clinical practice and represented a potential overdose.

Some previous studies have shown that midazolam has similar or shorter recovery than diazepam [15-16], but other studies have not [17]. Chung et al. assessed patients by tests requiring mental concentration and found that the early recovery was significantly quicker following diazepam than midazolam [18]. The rapid phase of disappearance of an agent related to distribution and the slow phase due to biotransformation of agent. The volumes of distribution of diazepam and midazolam are similar because both agents are equivalently lipophilic, then duration of action and initial recovery of both agents is similar [19]. Moreover, the volume of distribution is increased in female and obese patients. Zakko et al. exhibited that midazolam requirements were lower in men than in women [9]. Also, Masuda et al. found that loss of consciousness was more in male than female after midazolam administration and recall of pain was more common in female patients [20]. In octogenarian subjects volume of distribution of midazolam decreases and pharmacokinetics of this agent is influenced by age and elimination half life prolonged more than twofold compared to young patients that leads to reduced metabolic clearance [21].

Previous studies showed that midazolam/diazepam potency ratio was 3.4 [9] to 5 times [22]. Administration of both diazepam and midazolam intravenously in equipotent doses in volunteers depress ventilation similarly because of depression of the central respiratory drive [23]. Bell et al. showed that depression of minute ventilation after administration of diazepam and midazolam in equipotent odes was similar [24]. In other studies that evaluated the effect of diazepam and midazolam on PaCO2 and arterial blood gases, revealed no difference between two agents during conscious sedation [25]. It was found that injection of low dose of midazolam in conscious sedation does not affect ventilator response to CO2, therefore, in practical medicine respiratory depression with low dose of midazolam does not occur [26].

Zakko et al. identified that end-tidal CO2 was significantly higher from 5 to 45 minutes after midazolam than at a similar time after diazepam administration and showed that midazolam depressed ventilator drives more than diazepam [9]. However, this study showed that end-tidal CO2 60 to 70 minutes after diazepam administration was more than midazolam in similar time related to longer duration of action of diazepam. These findings support the importance of oxygenation monitoring in recovery unit in patients who received diazepam for sedation during operation [27].

Chung et al. suggested that oxygen saturation was never significantly decreased in patients who received diazepam and midazolam for conscious sedation during operation [18]. However, some studies identified that both diazepam and midazolam significantly decreased oxygen saturation and provided that the incidence and severity of hypoxemia were similar between two agents [9, 20, 24]. Moreover, the incidence of hypoxemia during operation in subjects who underwent conscious sedation with diazepam or midazolam was markedly reduced by administration of low flow of oxygen via nasal cannula [28-33]. The episode of apnea in our study was seen in 2 cases in diazepam and in 4 cases in midazolam group and was not statistically significant.

Chung et al. compared the degree of sedation in subjects who received diazepam and midazolam and showed significant difference between two agents at 5 and 10 minutes after administration. they revealed that patients who received midazolam were drowsier than those who received diazepam. However, at the end of operation or 30 minutes after procedure no differences in sedation were noted between two agents. He evaluated the psychomotor function of patients who received diazepam and midazolam by digit symbol substitution test (DSST) that is sensitive to central nervous system disruption and revealed that the performance returned to baseline at 60 minutes after diazepam administration and was significantly improved over baseline at 120 minutes, but deterioration persisted at 90 minutes after midazolam administration and returned to baseline at 180 minutes. Also they compared the sensory motor performance, a critical determinant of recovery between patients who received diazepam and midazolam and did not show any significant difference at any of the time during and after operation [18, 34]. In our study the level of sedation and surgeon's satisfaction was better in diazepam group compared to midazolam group. Moreover, the functional impairment during 24 hours after operation was not different between two groups. One of the major advantages of midazolam compared to diazepam is lower incidence of venous irritation due to thrombophelebitis. It was shown that venous sequelae occurred with similar frequency in patients who received diazepam versus midazolam for conscious sedation [18, 35]. In this study the tenderness at the site of injection was not statistically significant between two groups postoperatively.

Conclusion

Our study identify that equipotent doses of both diazepam and midazolam are effective for conscious sedation of patients who underwent cataract surgery. Diazepam produces better perioperative hemodynamic profile and less occurrence of apnea and decrease of oxygen saturation in patients who underwent cataract surgery compared to midazolam group. Diazepam produces better sedation and surgeon's satisfaction during operation compared to midazolam.

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