

# The Effects of Diazepam Administration on Hemodynamic Variables in Hypertensive Patients Who Undergoing Cataract Surgery

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**Background:** The purpose of this study was the evaluation of diazepam administration on perioperative blood pressure in hypertensive patients who undergoing cataract surgery.

**Methods:** Eighty controlled hypertensive patients who underwent cataract surgery under topical anesthesia and conscious sedation were enrolled in this study. All patients were randomly divided to two equal size group for administration of diazepam 0.05 mg/kg (n=40, diazepam group) and midazolam 0.01 mg/kg (n=40, midazolam group) in order to conscious sedation. The systolic and diastolic blood pressure, heart rate and oxygen saturation were recorded preoperatively as baseline value, and then 5, 10 and 15 minutes after diazepam or midazolam administration.

**Results:** There were no difference between two groups in terms of systolic, diastolic and heart rate preoperatively. Systolic and diastolic blood pressure was decreased significantly more in diazepam group compared to midazolam group perioperatively. Heart rate did not change significantly in both groups. Oxygen saturation of blood was decreased in both groups but not statistically significant. Systolic and diastolic blood pressure variability during each period intraoperatively was lower in diazepam group compared to another group. Systolic and diastolic blood pressure of patients during recovery room in diazepam group was lower than midazolam group.

**Conclusion:** In hypertensive patients who undergoing cataract surgery with topical anesthesia, administration of diazepam in order to conscious sedation is an effective and safe method with less perioperatively side effects.

**Keywords:** Diazepam; Midazolam; Cataract surgery; Hypertensive patients; Heart rate

Cataract surgery is widely performed using topical anesthesia and conscious sedation. This procedure is usually performed on octogenarian population and one third of these patients having concurrent disease such as hypertension [1]. It was shown that blood pressure increases during cataract surgery especially in female and decrease after procedure [2]. Benzodiazepines are widely used for conscious sedation in patients because of anxiolytic action, muscle relaxant and sedative properties. Moreover, administration of benzodiazepine intravenously sometimes induces hypotension that cause serious problem in medical practice [3]. The previous studies showed that the mechanism of hypotensive effect of benzodiazepine is controversial. Some studies reported that benzodiazepine act through arterial baroreflex [4], effect on sympathetic and vagal outflow [5], through its vasodilator effect [6] and its effect on the peripheral benzodiazepine receptors [7]. Also,

it was found that diazepam attenuates the plasma norepinephrine levels during operation [8]. The effects of benzodiazepine on sympathetic system and heart rate may be disruptive in patients with special situation such as hypovolemia and heart failure that needed sustained adrenergic activity to maintain hemodynamic stability [9]. However, diazepam has mild hemodynamic effects and widely used as a sedative agent in patients with cardiovascular disease [10]. When diazepam used with opioid, its hypotensive effects exacerbates and is associated with decreased levels of plasma catecholamines [11]. Moreover, the effects of diazepam on central autonomic reflexes are conflicting. Some studies showed decreased of baroreflex response of heart [12] and another study showed no alteration of baroreflex was observed 30 minutes after administration of low doses of diazepam [13]. According to previous studies, it seems that the use of diazepam in hypertensive patients may be a suitable drug for sedation. In octogenarian patients with coexisting disease, such as hypertension or cardiovascular disease, instability of blood pressure during operation may be dangerous. It is also assumed that the use of diazepam helps maintain blood pressure during surgery and reduces the need for administration of hypotensive medications. The purpose of this study is the evaluation of effects of diazepam administration on perioperative blood pressure in hypertensive patients who undergoing cataract surgery.

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## Methods

Eighty controlled hypertensive patients with mean age  $58.4 \pm 14$  (44 to 78) years who underwent cataract surgery under topical anesthesia and conscious sedation between October to December 2018 were enrolled in this study. Patients with systolic blood pressure more than 160 mmHg and/or diastolic blood pressure were more than 95 mmHg included in our study. Patients who underwent cataract surgery under general anesthesia, retrobulbar anesthesia or subjects with history of serious pulmonary, cardiac, central nervous system disease and uncontrolled hypertension were excluded from this study. A cardiologist visited all of our patients before operation in order to optimize antihypertensive regime. All patients received their antihypertensive medications approximately 3 hours before operation. We monitored all patients using electrocardiograph, noninvasive blood pressure monitor and a pulse oximeter during operation. Our hypertensive patients received  $1 \mu\text{g}/\text{Kg}$  fentanyl intravenously and were randomly divided by opening a sealed envelope to two equal size group for administration of diazepam 0.05 mg/kg (n=40, diazepam group) and midazolam 0.01 mg/kg (n=40, midazolam group) in order to conscious sedation. The systolic and diastolic blood pressure, heart rate and oxygen saturation were recorded preoperatively as baseline value, and then 5, 10 and 15 minutes after diazepam or midazolam administration intraoperatively. Sample size of our study was based on difference of 20 mmHg in blood pressure respectively, and a power of 0.8 and error of 0.05. Blood pressure and heart rate were tested using analysis of variance

repeated measures. Statistical comparisons were performed by analysis of variance (ANOVA), followed by student's t test. All values were expressed as mean  $\pm$  standard deviation. Significance was taken as p-value < 0.05.

## Results

Demographic data of both groups are summarized in (Table 1). There was no difference between two groups in terms of systolic, diastolic and heart rate preoperatively. Systolic and diastolic blood pressure was decreased significantly more in diazepam group compared to midazolam group during each period of the study in both groups. Heart rate did not change significantly either in diazepam group and midazolam group during each period of intraoperatively. Oxygen saturation of blood was decreased in both groups after administration of diazepam and midazolam during operation but not statistically significant (Table 2, 3). Systolic and diastolic blood pressure variability during each period intraoperatively was lower in diazepam group compared to another group (Figure 1-4). Two patients in diazepam group and four patients in midazolam group need antihypertensive agents for rising of blood pressure intraoperatively (p=NS). Therefore, stability of blood pressure during operation in diazepam group was more than another group and need to antihypertensive agent was less in diazepam group, but not statistically significant (p=0.12). Moreover, Systolic and diastolic blood pressure of patients during recovery room in diazepam group was lower than midazolam group.

**Table 1- Demographic data of diazepam and midazolam group**

Variables	Diazepam group (n=40)	Midazolam group (n=40)	P value
Age (yrs)	59.4 $\pm$ 12	58.16 $\pm$ 18	0.85
Weight (kg)	68.0 $\pm$ 18.4	69.4 $\pm$ 14.2	0.74
Sex (M/F)	18/22	21/19	0.66
ASA status	2.4 $\pm$ 0.4	2.3 $\pm$ 0.6	0.92

All variables are expressed as mean  $\pm$  SD.

**Table 2- Hemodynamic data and oxygen saturation in diazepam group**

Variables	Baseline	5 min	10 min	15 min	Recovery room
Systolic blood pressure (mmHg)	176 $\pm$ 8	149 $\pm$ 8*	151 $\pm$ 6*	151 $\pm$ 3*	154 $\pm$ 8
Diastolic blood pressure (mmHg)	103 $\pm$ 4	91 $\pm$ 5*	93 $\pm$ 4*	92 $\pm$ 6*	94 $\pm$ 4
Heart rate (beats/min)	71 $\pm$ 10	70 $\pm$ 8	74 $\pm$ 4	73 $\pm$ 10	74 $\pm$ 12
Oxygen saturation (%)	98.4 $\pm$ 1.2	96.2 $\pm$ 2.4	96.6 $\pm$ 2.1	97.1 $\pm$ 2.2	98 $\pm$ 1.6

All variables are expressed as mean  $\pm$  SD. \*: p<0.05 (5, 10 and 15 min versus baseline)

**Table 3- Hemodynamic data and oxygen saturation in midazolam group**

Variables	Baseline	5 min	10 min	15 min	Recovery room
Systolic blood pressure (mmHg)	170 $\pm$ 4	145 $\pm$ 10*	151 $\pm$ 3*	144 $\pm$ 7*	165 $\pm$ 4
Diastolic blood pressure (mmHg)	98 $\pm$ 8	86 $\pm$ 6*	89 $\pm$ 4*	88 $\pm$ 4*	96 $\pm$ 6
Heart rate (beats/min)	72 $\pm$ 8	73 $\pm$ 4	74 $\pm$ 6	72 $\pm$ 6	74 $\pm$ 8
Oxygen saturation (%)	98.8 $\pm$ 1.0	95.4 $\pm$ 1.0	96.2 $\pm$ 1.4	96.8 $\pm$ 1.8	98.4 $\pm$ 1.7

All variables are expressed as mean  $\pm$  SD. \*: p<0.05 (5, 10 and 15 min versus baseline)

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

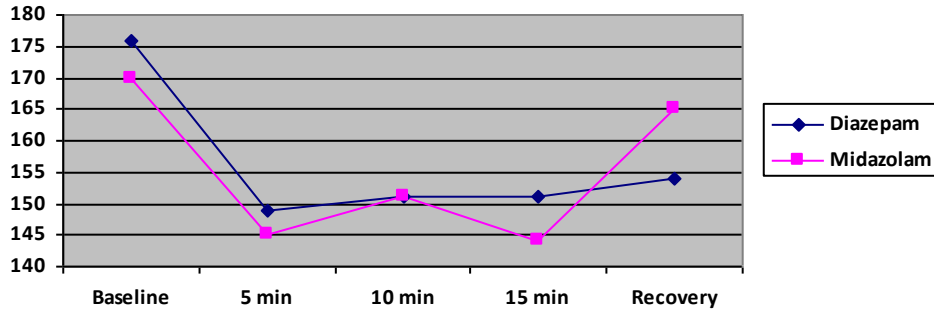


Figure 2- Comparison of diastolic blood pressure in diazepam and midazolam group

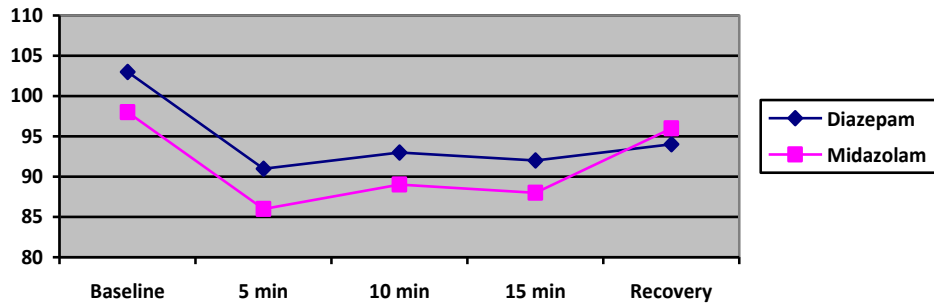


Figure 3- Comparison of heart rate in diazepam and midazolam group

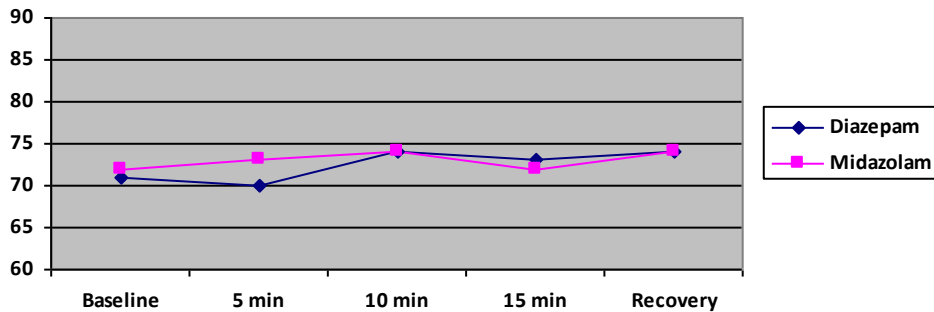
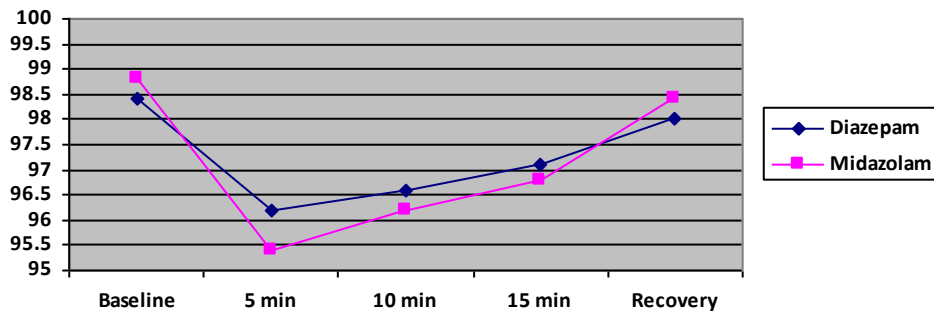


Figure 4- Comparison of oxygen saturation in diazepam and midazolam group



## Discussion

Cataract surgery is common perform in the world, and many of patients are elderly and have coexisting illness. Half

of these patients have hypertension [1]. On the other hand, hypertensive subjects perform cataract surgery twice more than other cases [14]. In many centers most cataract surgery is done under local anesthesia. Blood pressure rise during

this procedure because of pain, anxiety, discomfort and use of topical agents such as atropine and epinephrine. The anesthesiologist tries to keep blood pressure stable with administration of anesthetic agents such as benzodiazepine during and after operation. Diazepam is an old appropriate sedative agent that affects through gamma-aminobutyric acid (GABA) receptor and led to central nervous system depression [15]. In addition, diazepam has a hypotensive effect and the reason of this mechanism is controversial. The hemodynamic alteration of benzodiazepine mediated through effects on the sympathetic nervous system.

It was shown that benzodiazepine such as diazepam has depression effect on baroreflex function of heart and this effect is less marked than those observed with halogenated anesthetics. However, the depression effect of diazepam or midazolam on baroreflex control is similar to that observed with intravenous anesthetics [16]. Previous studies presented that both diazepam and midazolam produce alteration of baroreflex activity and a decrease of sympathetic activity [17]. Also, diazepam attenuates the plasma norepinephrine levels during operation [8]. Therefore, administration of diazepam or midazolam may be a potential hazard for intravenously induction of general anesthesia in subjects with acute hypovolemia. However, diazepam or midazolam through depression adrenergic activity may be considered as advantageous in the clinical management of patients with coronary artery disease [18]. On the other hand, it was shown that the observed decrease of sympathetic tone would have been expected to increase baroreceptor sensitivity [19]. Kitajima et al. found that systolic and mean blood pressure but not diastolic blood pressure after diazepam administration were significantly lower than those before its administration. However, heart rate did not change significantly [20]. Also, he evaluated the muscle sympathetic nerve activity (MSNA), the spontaneous activity of sympathetic postganglionic fibers that regulates peripheral vascular resistance and indicated that central cardiovascular regulatory mechanism was involved in the hypotensive action of diazepam. Moreover, no change in heart rate also supports this hypothesis, as peripheral hypotensive agents usually increase heart rate.

Another of the central hypotensive mechanisms of benzodiazepine is the involvement of hypothalamus. Local administration of GABA antagonists in close proximity of to the hypothalamus increase blood pressure, thus agonist such as diazepam would have reverse effect [21]. Moreover, Marty et al. identified that administration of diazepam and midazolam resulted in a significant decrease in plasma norepinephrine concentration. Plasma norepinephrine concentration is a reliable marker of adrenergic system and because of short half-life, it responds rapidly to changing stimuli. Moreover, he showed that plasma epinephrine concentration decreased significantly only in patients who received midazolam and diazepam administration had no effect on epinephrine concentration. He concluded that systolic blood pressure was decreased significantly in patients who received diazepam or midazolam, whereas diastolic blood pressure decreased only in subjects who received midazolam. Also, he indicated that decrease of sympathetic activity was more marked in patients with a high adrenergic activity such as hypertensive patients [18]. He could not explain the absence effect diazepam on epinephrine concentration. Like the different effect of midazolam and diazepam on concentration of

norepinephrine and epinephrine, different responses have been seen in thiopental administration [22-23]. Abel et al. confirmed the hypothesis of decrease of sympathetic activity after administration of diazepam regarding the vasodilator effect of diazepam [24-25]. Hoar et al. explained that combination of diazepam and morphine decreased the sympathetic nervous system activity that matches our results through the effect of diazepam and midazolam on blood pressure [11, 26-28].

## Conclusion

We found that systolic and diastolic blood pressure decreased after administration of diazepam and midazolam and the change of blood pressure after diazepam use was less than midazolam. We identified that the stability of hemodynamic variables was better after administration of diazepam compared to midazolam. Also, as previously mentioned the diastolic blood pressure decreased only after midazolam administration. Both diazepam and midazolam induce a sustained decrease of sympathetic tone and led to decreased of blood pressure during and after cataract surgery. The different hypotensive effect of diazepam and midazolam can be explained that the depression of baroreflex control on heart rate was more transient, so we think the sustained decreased effect of midazolam and especially diazepam on blood pressure related to decrease of norepinephrine concentration. Moreover, since diazepam does not have an effect on epinephrine concentration, its blood pressure changes are likely to occur at a lower rate than midazolam. We concluded that in hypertensive patients with high adrenergic system activity, administration of diazepam is effective and safer than midazolam administration and the hemodynamic of these patients remains more stable perioperatively

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