ORIGINAL ARTICLE

Effects of sedation with midazolam or propofol infusion on stress hormone and heart rate variability in spinal anesthesia

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ABSTRACT

Objective: Sedation with midazolam or propofol have effects on sympathetic and parasympathetic activity during spinal anesthesia by removing the factor of anxiety and stress. The present study was conducted to compare the effects of sedation with midazolam and propofol on cardiac sympathetic and parasympathetic activity as well as stress hormone in patients having spinal anesthesia.

Methodology: This randomized controlled non-blind study was conducted at operating room in the city hospital. Sixty patients, aged 30 to 70 years, with ASA physical status I or II, scheduled for spinal and epidural anesthesia for lower extremity surgery were enrolled for the study. After an epidural catheter insertion, spinal anesthesia was performed at L4/5 with 0.5% tetracaine 8 to 12 mg. Oxygen was administered at 6 L/min by a mask. After surgery started, midazolam infusion was started at 0.6 mg/kg/h for 1.5 min, then changed to 0.15 mg/kg/h, and stopped at the end of surgery in the midazolam group. In the propofol group, propofol infusion was started at 10 mg/kg/h then changed to 5, and 2.5 mg/kg/h every one minute. In the control group, no sedative was administered. Blood pressure, heart rate, respiratory rate, percutaneous oxygen saturation, end-tidal carbon dioxide pressure, sedation level, bispectral index, plasma concentrations of epinephrine, norepinephrine, and cortisol, and hear rate variability were measured.

Results: Blood pressure decreased significantly in all groups without any inter group differences. Heart rate decreased significantly in all groups, and the decrease was the largest in the propofol group. Plasma concentrations of epinephrine and norepinephrine decreased significantly in the propofol group. Both high frequency component (HF) and low frequency component (LF)/HF ratio in heart rate variability decreased significantly in all groups. HF and LF/HF were significantly lower in the propofol and midazolam groups than those in the control group. LF/HF was significantly lower in the propofol group than that in the midazolam group.

Conclusion: Spinal anesthesia decreased cardiac sympathetic and parasympathetic activity with larger decrease in sympathetic activity. Sedation with continuous infusion of midazolam or propofol further decreased these activities, with propofol exerting a more pronounced effect as compared to midazolam.

Key words: Spinal anesthesia; Sedation; Moderate Sedation; Deep Sedation; Midazolam; Propofol; Heart rate variability; Catecholamines

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INTRODUCTION

During spinal anesthesia, many patients prefer to be asleep. For sedating the patients without putting them to an anesthetized state, midazolam or propofol have been widely used. The author had already investigated the optimal infusion doses of midazolam[1] and propofol[2] according to the sedation level, hemodynamics and respiration, the results of which were published in 2004 and 2007 respectively.

In spinal anesthesia, hypotension or bradycardia often occurs due to inhibition of sympathetic activity with preserved parasympathetic activity, which rarely culminates in cardiac arrest.[3] Sedation with midazolam or propofol might add some effects on sympathetic

and parasympathetic activity during spinal anesthesia. The present study was performed to compare the effects of sedation with midazolam and propofol on cardiac sympathetic and parasympathetic activity as well as stress hormone in patients, who received spinal anesthesia.

METHODOLOGY

After the approval of the protocol by the institutional ethics committee and informed consent from patients, 60 patients, aged 30 to 70 years, with ASA physical status I or II, scheduled for spinal and epidural anesthesia for lower extremity surgery were enrolled in the study. Those, who had cardiac, respiratory, liver, renal or brain disease, who were obese (body mass index >30), who were habitual sedatives abusers before surgery, or who had asthma or allergy to study drugs or their constituents, were excluded. The patients were randomly divided into three groups; midazolam group and propofol group to receive midazolam and propofol respectively, and the third group as control group, which did not receive any sedative drug.

As a premedication, midazolam 2 – 3 mg was administered intramuscularly 15 to 30 min before entering the operation room. An epidural catheter was inserted into one of the interspace between L1 and L4 so as to use epidural anesthesia in case of failure or time up of the spinal anesthesia in lateral position. Then spinal anesthesia was performed at L4/5 with 0.5% tetracaine 8 to 12 mg. Anesthesia level was checked with cold sensation 5 min after spinal anesthesia in supine position. Oxygen was administered at 6 L/min by a mask. After surgery started and it was confirmed that patients had no pain, in the patients belonging to the midazolam group, midazolam infusion was started at 0.6 mg/kg/h for 1.5 min, then the rate reduced to 0.15 mg/kg/h, and stopped at the end of surgery.[1] In the propofol group, propofol infusion was started at 10 mg/kg/h, then reduced to 5 mg/kg/h after one minute and 2.5 mg/kg/h after second minute.[2] In the control group, no sedative was administered. Radial artery was cannulated to measure plasma concentrations of catecholamines, and cortisol.

Blood pressure, heart rate, respiratory rate, percutaneous oxygen saturation (SpO_2), end-tidal carbon dioxide pressure ($EtCO_2$), sedation level, bispectral index (BIS), plasma concentrations of epinephrine, norepinephrine, and cortisol, and heart rate variability were measured. Sedation level was assessed by modified Observer's Assessment of Alertness / Sedation (OAA/S) score.[4] BIS was measured with BIS A-1050™ (Aspect Medical Systems, Newton, USA).

Plasma concentrations of epinephrine, norepinephrine, and cortisol were measured with high performance liquid chromatography (HLC-8030™, Toso, Tokyo, Japan) at BML laboratory (Tokyo, Japan). Heart rate variability was measured with LRR-03™ (GMS, Tokyo, Japan) and analyzed with Mem Calc™ (Suwa Trust, Tokyo, Japan).

Power analysis was performed to detect the inter- group differences of low frequency component (LF) and LF/ high frequency component (HF) with power of 0.80 and effect size of 0.3 using the G Power™ software (University Mannheim, Germany).

Statistical analysis was performed with factorial analysis of variance and chi-square test for demographic data, and repeated measures ANOVA for measured parameters followed by Student-Neuman-Keuls test as a post hoc analysis. The p value less than 0.05 was considered to be statistically significant.

RESULTS

The power analysis showed that 60 patients were necessary. Therefore, we included 20 patients in each group. Demographic data were not different among the three groups (Table 1).

Blood pressure decreased significantly during surgery in all groups without any inter group differences. Heart rate decreased significantly in all groups, and the

Table 1: Demographic data

Demographic parameter	Propofol group	Midazolam group	Control group
Age (years)	55 ± 13	61 ± 8	57 ± 10
Gender (Male/Female)	11/9	12/8	9/11
Body weight (kg)	57 ± 12	58 ± 10	63 ± 9
Height (cm)	163 ± 14	162 ± 11	164 ± 10
Duration of surgery (min)	224 ± 51	185 ± 39	201 ± 43
Level of spinal anesthesia	T7 ± 3	T6 ± 2	T7 ± 3

Mean ± standard deviation (SD) or number of patients are shown.

Table 2: Hemodynamics, respiration, and sedation

Parameters	Groups	Before surgery	10 min	30min	60 min	End of surgery	30 min
Systolic blood pressure (mmHg)	C	132 ± 10	119 ± 11*	117 ± 11*	121 ± 10*	130 ± 10	127 ± 12
	P	136 ± 14	110 ± 10*	112 ± 10*	113 ± 10*	125 ± 9	126 ± 10
	M	135 ± 13	112 ± 9*	110 ± 11*	114 ± 11*	128 ± 10	123 ± 12
Heart rate (beats/min)	C	79 ± 8	77 ± 9	73 ± 6*	72 ± 7*	75 ± 6	76 ± 8
	P	78 ± 7	63 ± 7*,+,++	60 ± 8*,+,++	62 ± 8*,+,++	65 ± 9*,+,++	75 ± 9
	M	76 ± 8	78 ± 9	70 ± 7*	71 ± 8*	73 ± 8	74 ± 8
Respiratory rate (breaths/min)	C	14 ± 2	13 ± 3	12 ± 3	12 ± 3	14 ± 2	14 ± 3
	P	14 ± 3	10 ± 2*,+,++	9 ± 2*,+,++	10 ± 2*,+,++	10 ± 2*,+,++	15 ± 4
	M	15 ± 3	12 ± 3*	11 ± 2*	12 ± 3	13 ± 3	15 ± 3
SpO_2 (%)	C	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1
	P	100 ± 0	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1
	M	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1
$EtCO_2$ (mmHg)	C	34 ± 2	35 ± 3	35 ± 4	35 ± 3	34 ± 3	35 ± 2
	P	35 ± 3	35 ± 4	36 ± 3	36 ± 3	36 ± 3	35 ± 2
	M	33 ± 2	35 ± 3	36 ± 3	35 ± 2	35 ± 2	34 ± 2
Sedation score	C	4.5 (3-5)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	4 (3-5)
	P	4 (3-5)	1.5 (1-2)*,+	1.5 (1-3)*,+	2 (1-3)*	2.5 (1-4)*	3 (2-5)
	M	4 (3-5)	1.5 (1-3)*,+	2 (1-3)*,+	2.5 (1-3)*	2.5 (1-4)*	3 (2-5)
BIS	C	93 ± 8	86 ± 9	84 ± 8*	82 ± 9*	90 ± 7	92 ± 8
	P	96 ± 7	68 ± 8*,+,++	62 ± 9*,+,++	63 ± 8*,+,++	77 ± 7*,+	90 ± 9
	M	94 ± 8	79 ± 9*,+	70 ± 8*,+	73 ± 8*,+	74 ± 8*,+	87 ± 9

Mean ± SD or median and ranges are shown. BIS, bispectral index; Mean ± standard deviation or median and range in the parenthesis (sedation score) are shown. Modified Observer's Assessment of Alertness / Sedation score (OAA/S) is used for sedation score (14); 5, responds readily to name spoken in normal tone; 4, Lethargic response to name spoken in normal tone; 3, responds only after name is called loudly or repeatedly; 2, responds only after mild pudding or shaking; 1, does not respond to mild prodding or shaking; 0, does not respond to noxious stimulation. : $P < 0.05$ vs. the value before surgery, $^{+}$: $P < 0.05$ vs. the Control group, $^{++}$: $P < 0.05$ vs. the Midazolam group. Groups C-Control; P-Propofol; M-Midazolam

Table 3: Plasma concentration of catecholamines, and cortisol

Hormone	Group	Before infusion	30 min	60 min	At the end of infusion	30 min
Epinephrine (ng/mL)	C	0.070 ± 0.034	0.061 ± 0.042	0.058 ± 0.038	0.056 ± 0.041	0.058 ± 0.039
	P	0.072 ± 0.033	0.035 ± 0.040*,+	0.022 ± 0.023*,+	0.032 ± 0.040*,+	0.054 ± 0.042
	M	0.070 ± 0.041	0.046 ± 0.042*	0.042 ± 0.043	0.048 ± 0.038*	0.044 ± 0.041*
Norepinephrine (ng/mL)	C	0.095 ± 0.075	0.086 ± 0.071	0.082 ± 0.075	0.095 ± 0.081	0.125 ± 0.112
	P	0.085 ± 0.060	0.060 ± 0.050*,+,++	0.023 ± 0.021*,+,++	0.030 ± 0.014:,+,++	0.088 ± 0.090
	M	0.090 ± 0.070	0.075 ± 0.065	0.077 ± 0.052	0.110 ± 0.075	0.131 ± 0.100
Cortisol (ng/mL)	C	132 ± 87	135 ± 100	154 ± 113	158 ± 114	166 ± 106
	P	121 ± 69	123 ± 92	135 ± 105	158 ± 130	168 ± 111
	M	125 ± 75	126 ± 98	167 ± 110	175 ± 105	170 ± 112

Mean ± SD are shown. No differences are seen between the groups and intra groups. Groups C-Control; P-Propofol; M-Midazolam
*: $P < 0.05$ vs. the value before surgery, $^{+}$: $P < 0.05$ vs. the Control group, $^{++}$: $P < 0.05$ vs. the Midazolam group

decrease was the largest in the propofol group (Table 2). Respiratory rate decreased significantly in the midazolam and propofol groups with larger decrease in the propofol group (Table 2). SpO_2 and $EtCO_2$ did not change significantly in all groups. Sedation score decreased significantly in the midazolam and propofol groups without any differences between the two groups (Table 2). BIS decreased significantly in all groups with the largest

Table 4: Heart rate variability

	Groups	Before surgery	10 min	30min	60 min	End of surgery	30 min
HF (power msec·msec)	C	24.0 ± 7.5	15.0 ± 7.7*	9.1 ± 6.4*	9.2 ± 4.9*	10.9 ± 6.1*	11.8 ± 5.2*
	P	21.3 ± 6.9	8.8 ± 4.2*,+	6.3 ± 4.0*,+	5.8 ± 3.5*,+	6.7 ± 4.0*,+	8.9 ± 6.5*,+
	M	20.5 ± 7.8	10.8 ± 6.2*	8.2 ± 8.0*	7.0 ± 5.0*,+	7.5 ± 6.0*,+	10.5 ± 6.8*
LF/HF	C	7.8 ± 2.4	3.3 ± 0.8*	2.9 ± 0.4*	2.5 ± 0.9*	2.4 ± 0.7*	2.3 ± 1.0*
	P	7.9 ± 3.3	1.4 ± 1.0*,+,++	1.2 ± 0.9*,+,++	1.3 ± 0.8*,+,++	1.3 ± 0.9*,+,++	2.0 ± 1.0*
	M	8.7 ± 3.5	2.3 ± 1.8*	2.1 ± 1.1*	2.3 ± 1.2*	2.2 ± 1.0*	2.2 ± 1.1*

Mean ± SD are shown. Groups C-Control; P-Propofol; M-Midazolam
*: P < 0.05 vs. the value before surgery, $^{+}$: P < 0.05 vs. the Control group, $^{++}$: P < 0.05 vs. the Midazolam group

decrease in the propofol group (Table 2).

Plasma concentrations of epinephrine and norepinephrine decreased significantly in the propofol group (Table 3). Plasma cortisol concentration did not change in all of the groups (Table 3).

Both HF and LF/HF ratio decreased significantly in all groups (Table 4). HF and LF/HF were significantly lower in the propofol and midazolam groups than those in the control group (Table 4). LF/HF was significantly lower in the propofol group than that in the midazolam group (Table 4).

DISCUSSION

The present results showed that all groups had decreased HF and LF/HF and the decrease in LF/HF was larger than that in HF with the largest difference with propofol. The decrease in HF and LF/HF was larger with propofol than control and midazolam. Only propofol decreased plasma concentrations of epinephrine and norepinephrine.

We administered midazolam as a premedication in all groups. It reduced the increased sympathetic activity before surgery in the elderly.[5] Therefore, it might decrease the difference among the groups, while our patients were younger than the elderly patients studied by Ikeda et al.[5]

We used constant infusion of midazolam[1] and propofol[2] at decreasing rates in all patients in each group according to our previous results providing optimal sedation in spinal anesthesia, while BIS was different between midazolam and propofol groups in the present study. However, sedation scores were not different between the groups, therefore, clinically both of the groups might be comparable.

HF reflects respiratory related parasympathetic activity, and LF reflects cardiac parasympathetic and sympathetic activity, therefore, LF/HF shows sympathetic activity.[6] Ventilatory depression such as tidal volume reduction would decrease LF then LF/ HF.[7] Respiratory rate was decreased more with propofol than with midazolam and control in the present study. Therefore, it might add some effects on decreased LF/HF with propofol.

In spinal anesthesia, many different effects were observed in sympathetic and parasympathetic activity. Carpenter et al[3] reported that sympathetic activity might decrease with preserved parasympathetic activity.[3] However, some studies showed no changes in LF and LF/HF,[8,9] or unchanged cardiac sympathetic-parasympathetic balance.[10] Others reported increased parasympathetic activity,[11] or sympathetic predominance.[12] Introna et al[13] showed that increasing the level of spinal anesthesia above T4, both LF and HF decreased with no change in LF/HF.[13] Our present study showed that plasma catecholamine concentrations did not change, but both HF and LF/HF decreased in spinal anesthesia. Therefore, after premedication with midazolam, spinal anesthesia itself did not change systemic sympathetic activity, while decreased cardiac sympathetic and parasympathetic activity.

There are many studies to show the effects of midazolam on heart rate variability with different results. Midazolam decreased total power of heart rate variability.[14] This is consistent with our results. However, HF decreases[14-17] or increases,[9] and LF/HF decreases,[7,9] increases,[18] or does not change.[16,17] The results might depend on the dose. Intravenous midazolam 5 mg decreased HF and increased LF, but not 1 mg.[18] Midazolam increases HF with very high doses,[14] but increases LF/HF with low doses.[16,19] The infusion dose in our study is relatively high, and both HF and LF/HF decreased, which might have included the effects of spinal anesthesia. Sedation with midazolam decreased epinephrine and norepinephrine concentrations.[20] However, it is reported that in ventilated patients, sedation with midazolam did not change plasma epinephrine and norepinephrine concentrations.[21] Our results agree with the latter, probably because premedication with midazolam already decreased control concentrations. Therefore, in spinal anesthesia, midazolam had no influence on systemic sympathetic activity, but decreased cardiac sympathetic

and parasympathetic activity, especially sympathetic activity if continuously used after premedication with midazolam.

Propofol decreased total power, LF, HF, and increased LF/HF.[22,23] Riznyk et al[24] reported that propofol decreased HF and preserved LF, which indicates increased LF/HF. Both showed that cardiac parasympathetic activity decreased and sympathetic activity increased as shown by Kanaya et al.[25] Adding infusion of propofol further decreased total power and LF, but not HF, which shows parasympathetic activity increased.[22] Hidaka et al[9] showed that propofol decreased LF and LF/HF with no change in HF in spinal anesthesia. Our results showed propofol decreased both HF and LF/HF with larger decrease in LF/HF. Therefore, propofol might have parasympathetic dominance. Thus, our results were consistent with the study of infusion of propofol.[22] Propofol decreased epinephrine and norepinephrine concentrations in the study by Oei-Lim et al,[20] which is consistent with our present results.

Tsygayasu et al[26] reported that the changes in LF, HF, and LF/HF were smaller with midazolam than propofol. Our results also showed propofol reduced HF and LF/HF than midazolam. In addition, the ratio of the decrease of LF/HF and HF was larger with propofol than midazolam in the present study. Therefore, propofol depressed cardiac sympathetic and parasympathetic activity, especially sympathetic activity more than midazolam.

CONCLUSION

In conclusion, spinal anesthesia decreased cardiac sympathetic and parasympathetic activity with larger decrease in sympathetic activity. Sedation with continuous infusion of midazolam or propofol further decreased these activities with larger effects with propofol. Propofol also decreased systemic sympathetic activity.

Conflict of interest: None

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★★★★★

My Most Memorable Patient

The patient with an absent gall bladder

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It was 1993 that we started Laparoscopic cholecystectomies at KRL hospital Islamabad. The patients showed great enthusiasm to accept this new modality of treatment. Among them was a beautician running a beauty salon in a nearby residential sector. She had had a long history of biliary symptoms; had been advised by doctors to have her gall bladder (GB) removed, but was reluctant to have it done due to expected big abdominal scar it would leave.

An upper abdominal ultrasound report stated '*contracted GB with no stones*'. The radiologist advised a repeat ultrasound after proper fasting the following week. Repeat report showed '*contracted GB with no stones*'. Hence an oral cholecystogram was requested, the report of which showed '*non-functioning GB'.*

After explaining the pros & cons of the surgery she agreed to have a lap chole and was put for surgery on the next available operating list. After abdominal insufflation with CO_2 we tried to locate the GB. We struggled for approximately half an hour with blunt dissection of whatever we thought could be a GB but failed to identify the structure positively. Ultimately we had to proceed with open cholecystectomy. During this time our anesthetist casually passed a remark that it may be 'a case of congenital absence of GB'. It drew my attention to the fact that it might well be the case and I started to think on those lines.

When we opened the abdomen I found to my horror that the structure we were dissecting for a gall bladder was actually the *porta hepatis*. Luckily we didn't cut or damage anything in that area. We started to look for the possible GB sites in the abdomen for a case of congenital absence of GB but failed to identify any such structure. Therefore, we closed the abdomen.

Her postop recovery was quite smooth and uneventful, but she was very disappointed to see the big cut in her abdomen. For some reason her symptoms of biliary colic resolved and when I last saw her a few years later, she was asymptomatic. The only question she asked me and our female theatre staff whenever they went to her salon for her services was, "If my gall bladder was absent from birth why did you have to open my tummy". I am still looking for an answer to her question.