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Research Article

Comparison of the Effect of Propofol and Midazolam on Cognitive Performance in Elderly Patients Undergoing Spinal Anesthesia: A Double-Blind Clinical Trial

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ABSTRACT

Background: The effects of anesthetics on memory have not yet been completely clear, and there have been some discrepancies on this issue in the literature. This study aimed to compare the effect of two sedatives, Propofol and Midazolam, on the incidence of cognitive dysfunction in elderly patients undergoing spinal anesthesia.
Methods: This double-blind clinical trial was conducted on 136 elderly patients who underwent spinal anesthesia in Besat Hospital, Hamadan, Iran, during 2020-21. The patients were randomly assigned into two groups of Propofol (0.2 mg/kg) and Midazolam (0.02 mg/kg). The Wechsler Memory Scale-III (WMS-III) were utilized to assess the cognitive dysfunction and memory coefficient in the two groups.
Results: There was no significant difference between the two groups in terms of short and long-term memory, as well as cognitive dysfunction before and after spinal anesthesia (P>0.05). The time of onset of sedation (Z=-11.11; P<0.005) and recovery from sedation (Z=-10.56; P<0.005) were longer in the Midazolam group, compared to the Propofol group. There were no significant differences between the two groups before and after operation regarding the WMS-III categories (P>0.05). The comparison of the two groups in terms of memory coefficient after operation showed no significant differences between them in this regard (Z=-0.63; P=0.52).
Conclusion: Midazolam and Propofol showed no differences regarding the effects on the postoperative memory coefficient or cognitive dysfunction.

Postoperative cognitive dysfunction (POCD) is a serious problem in elderly patients undergoing major surgeries, which can last 1-12 months or longer [1]; accordingly, its incidence has been reported to be prevalent in 7%-75% of the patients [2]. The pathogenesis of POCD is not clear. Intravenous and inhaled anesthetics, opioids, benzodiazepines, and anticholinergics are the suspected risk factors for POCD [3].

Today, the use of regional anesthesia techniques, is preferred to general anesthesia,especially in lower extremity surgeries due to simple technique, complete sensory and motor block, faster onset of action, and less postoperative side effects [3-4]. In recent years, concerns have been raised over the effects of general anesthesia and spinal anesthesia on long-term memory impairment, especially in elderly patients [5].

One of the relatively common surgeries in elderly individual is lower extremity fracture surgery, which is usually performed under spinal anesthesia. Although the spinal anesthesia technique reduces the need for consuming many medications, it increases the use of sedation, especially in elderly patients to withstand the surgery duration [6-7].

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There are different medications to provide sedation in spinal anesthesia, the most common of which are Midazolam and Propofol. Midazolam is a short-acting benzodiazepine that has various hypnotic, sedative, amnestic, anticonvulsant, and anti-anxiety effects [8]. The main benefits of Propofol include the rapid onset of action, lack of active metabolites, and rapid liver metabolism [9-10]. The effects of anesthetics on memory have not yet been completely clear, and there are some disagreements on the issue in the literature [9]. Therefore, this study aimed to compare the effects of two sedatives, namelyPropofol and Midazolam, used in spinal anesthesia on the incidence or progression of cognitive dysfunction in elderly patients undergoing orthopedic surgeries.

Methods

This prospective randomized double blind, controlled clinical trial study was conducted in Besat hospital in Hamadan, Iran, between 2020 and 2021.The protocol study was approved by the Research Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran (IR.UMSHA.REC.1397.966). This study Registered at Iranian Registry of Clinical Trials (IRCT20120915010841N19). The study was conducted in accordance with the Declaration of Helsinki and subsequent. Before the study, sufficient information was given to the patients; moreover, they were assured in terms of data confidentiality. Written informed consent were obtained from all patients, and they were assured that they could leave the study at any time.

Patients older than 65 years, candidate for lower limb surgery under spinal anesthesia, and physical status(ASA) class I and II, were enrolled in this study. Any patients not willing to participate or continue the study, and those who had an allergy to anesthetics and sedatives, as well as a history of alcohol and drug consumption (sedatives and anticonvulsants) and presence of any contraindication for spinal anesthesia including with spinal deformities, inability to maintain the required body position during needle puncture, elevated intracranial pressure, localized infection at the site of needle insertion, low platelet count and hypovolemia, were excluded from the study. Patients with failure of spinal anaesthesia who were under general anesthesia were removed from the study.

The sample size of this study was calculated based on previous studies was conducted by Yaraghi et al. [11], the error coefficient of 0.05 and power of 80%. The sample size was calculated at 136 cases (68 cases in each group).

Patients older than 65 years with the ASAclass of I and II who were candidates for lower limb surgery under spinal anesthesia were randomly assigned to the Group A(Propofol) or B(Midazolam). After spinal anesthesia with hyperbaric 0.5% bupivacaine patients received in Group A, 0.2 mg/kg Propofol (10mg⁄ml,20mlAmp, B.Braun Co.Germany) and in Group B, 0.02 mg/kg Midazolam (5mg⁄1ml Amp, Aburaihan Co.Iran) intravenously. The medications were prepared into syringes with similar sizes and shapes and labeled as A and B by an anesthesia nurse who was unaware about study protocol.

At first, demographic characteristics of patients, including age, gender, education level, marital status, and type of surgery were recorded in a researcher-made checklist. Before the spinal procedure, patients received 7 ml/kg ringer serum. Then,10 mg of bupivacaine 0.5% and 2.5 µg Sufentanil were injected into the subarachnoid space for all patients in a sitting position and the patients were turned to the supine position. After spinal anesthesia and before surgery, 0.2 mg/kg Propofol and 0.02 mg/kg Midazolam, that prepared into similar syringes and labeled as A and B were intravenously administered to groups A and B, respectively. The anesthesiologists and nurses who completed the data collection forms were blinded to the group allocated of patients.

The patients were monitored using electrocardiography, pulse oximetry, and a non-invasive blood pressure Monitoring (Saadat Model:162, Iran). Before and after anesthesia, the clinical variables including systolic and diastolic blood pressure, mean arterial pressure, heart rate, respiratory rate, and oxygen saturation in various times were measured and recorded every 3 min to 20 min and then every 10 min until the end of the operation.

In case of hypotension (systolic blood pressure less than 90 mmHg) and bradycardia (heart rate less than 50 beats per min), 10 mg of ephedrine and 0.5 mg of atropine were administered intravenously. The incidence of nausea and vomiting during the operation, sedation score, onset time of sedation and recovery from sedation, anesthesia and surgery duration were evaluated by the anesthesia assistant and recorded in a form.

Wechsler Memory Scale-III (WMS-III) was utilized to assess the cognitive dysfunction in the cases receiving surgical operation. The WMS-III is a composite test that is performed individually and designed to better understand different parts of a patient's memory. This scale provides the full range of memory functions and has been carefully designed based on the latest existing memory theories. The scale was completed for all patients before and after anesthesia.

The obtained data were recorded and analyzed in SPSS software (version 23). Furthermore, quantitative and qualitative data were described using frequency (percentage) and mean (±SD), respectively. The normality of the data was assessed using the Kolmogorov-Smirnov test. In addition, the t-test and its nonparametric equivalent (Mann-Whitney U test) were used to compare the data between the two groups. Paired t-test and its nonparametric equivalent were employed to compare the data before and after the operation. The homogeneity of the stratified data between the two groups was determined using the Chi-square test. Moreover, a correlation coefficient was employed to

assessthe relationship between the variables. A p-value less than 0.05 was considered statistically significant.

Results

In total, 136 patients were included in this study (Figure 1) with the mean age of 69.65±5.4 years; moreover, the majority (60.3%) of the cases were male.In addition, the mean ages of the patients in the Midazolam and Propofol groups were estimated at 69.91±5.81 and 69.4±5 years, respectively. The comparison between the two groups in terms of age showed no significant difference between them (Z=-0.22; P=0.82). It should be noted that all patients were married. (Table 1) tabulates the comparison between the two groups in terms of other demographic characteristics and some clinical findings.

The two groups were also compared in terms of duration of cognitive dysfunction, short-term memory pre and post spinal anesthesia, long-term memory pre and post spinal anesthesia, as well as preoperative and POCD (Table 2). Based on the obtained results, there was no significant difference between the two groups in terms of short- and long-term memory before spinal anesthesia (P>0.05). Moreover, the score of cognitive dysfunction was not significantly different between the two groups (Z=-0.05; P=0.95). However, the duration of cognitive dysfunction was longer in patients in the Propofol group, compared to that in the Midazolam group.

The comparison of short-term memory before and after spinal anesthesia showed a significant difference between them (Z=-4.704; P<0.005); however, there was no significant difference pre and post spinal anesthesia regarding long-term memory (Z=-1.084; P=0.08). On the other hand, a significant difference was reported between preoperative and POCD (Z=-5.86; P<0.005). The comparison between the two groups separately showed a significant difference between preoperative and POCD in the Propofol group (Z=-1.99; P=0.04), not in the Midazolam group (Z=-0.41; P=0.67).

(Figure 2) presents the change process of systolic and diastolic blood pressure(SBP&DBP), mean arterial pressure(MAP), heart rate(HR), respiratory rate(RR), and oxygen saturation(SPO2) at various times. The two groups were compared at different times in terms of the afore mentioned variables. Based on the obtained results, there was no significant difference between the two groups regarding systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation before anesthesia and at different times after anesthesia (P>0.005). Moreover, no significant difference was found between the two groups in terms of mean arterial blood pressure at different times, except for immediately after injection of propofol (Z=-1.96; P=0.03). The sedation score was significantly different between the two groups before anesthesia and at different times after anesthesia (P<0.05).

The mean onset and recovery time of sedation, anesthesia duration, and surgery duration is shown in (Table 3). According to the results, the two groups are not different in terms of anesthesia duration (Z=-0.78; P=0.97) and surgery duration (Z=-0.03; P=0.43). However, the time of onset (Z=-11.11; P<0.005) and recovery from sedation (Z=-10.56; P<0.005) were longer in the Midazolam group, compared to the Propofol group.

(Table 4) presents the comparison of Midazolam with Propofol pre and post operation regarding WMS-III categories, which showed no significant differences between the two groups in this regard (P>0.05). In general, the mean values of pre- and post-operative memory coefficients were determined at 73.04±13.11 and 76.48±12.35, respectively. Before the operation, the mean memory coefficients in the Midazolam and Propofol groups were 72.71±14.104and 73.36±12.13, respectively. Furthermore, the mean of post-operative memory coefficient in the Midazolam and Propofol groups were obtained at 75.61±12.22 and 77.35±12.502, respectively. There was no significant difference between the two groups in terms of pre-operation memory coefficient (Z=-0.078; P=0.93).

The comparison of the two groups in terms of memory coefficient after operation showed no significant difference between the two groups (Z=-0.63; P=0.52). Moreover, there was no correlation between the time of anesthesia and memory coefficient before (r=-0.04; P=0.58) and after the operation (r=-0.002; P=0.98).

Additionally, there was no difference between the two surgery duration lengths (higher and lower than 90 min) in terms of memory coefficient score before (Z=-0.55; P=0.57) and after the operation (Z=-0.84; P=0.39). There was also no difference between males and females in terms of memory coefficient before (Z=-1.25; P=0.21) and after the operation (Z=-1.23; P=0.21). A correlation was noted between age and memory coefficient before (r=-0.21; P=0.01) and after operation (r=-0.28; P=0.001), memory coefficient before (Z=-3.42; P=0.001) and after the operation (Z=-4.24; P<0.005) was higher among patients younger than 70 years of age, compared to those who were older than 70 years.

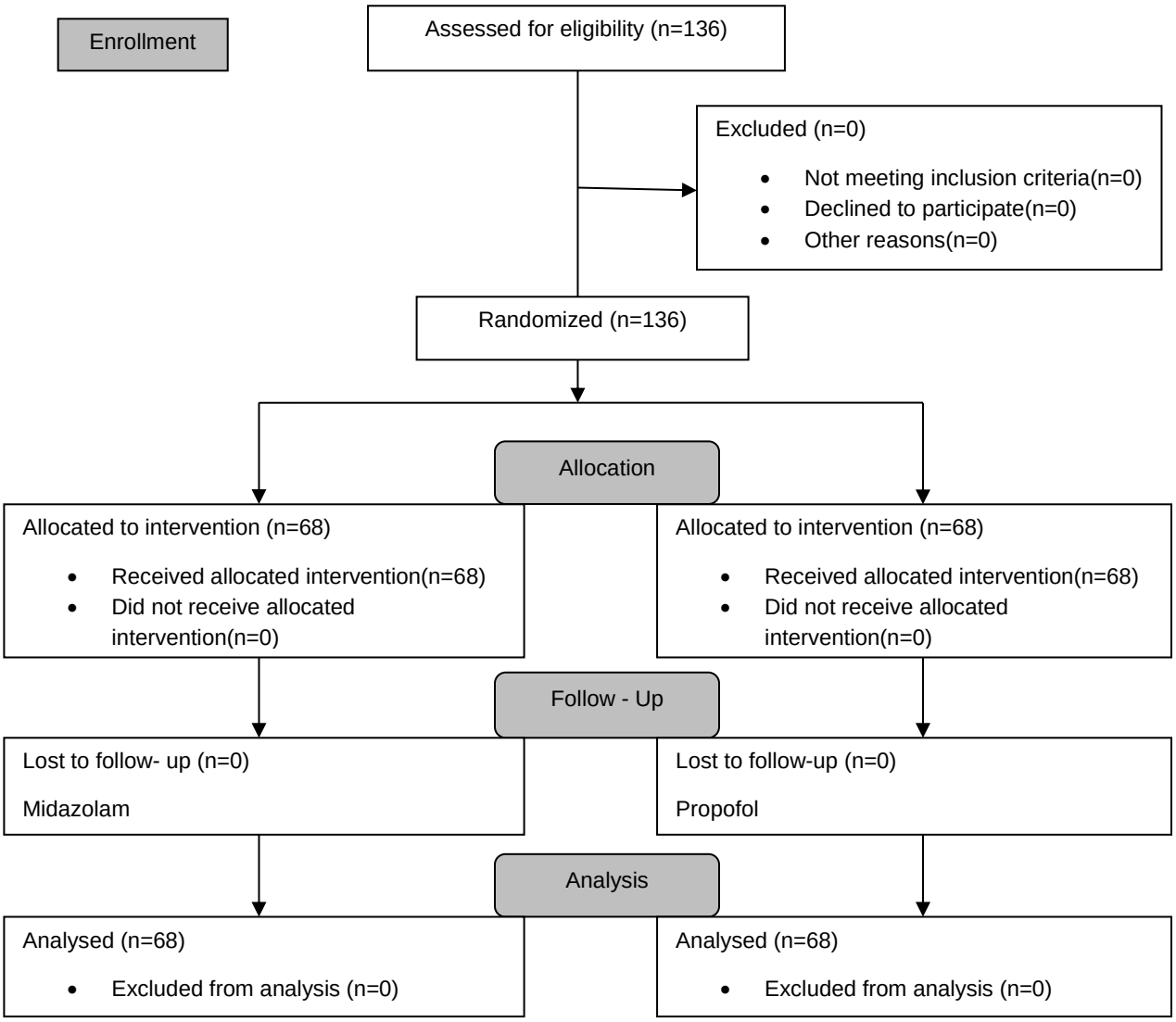


Figure 1- Flowchart of the trial (Consort Chart)

Table 1- Comparison of demographic characteristics and clinical findings in two groups

Variables		Midazolam		Propofol		Total		$\chi 2$	P value
		Mean	SD	Mean	SD	Mean	SD		
Gender	Male	37	54.4	45	66.2	82	60.3		
	Female	31	45.6	23	33.8	54	39.7	1.96	0.16 NS
Education level	Illiterate	38	55.9	35	51.5	73	53.7		
	Primary school	21	30.9	18	26.5	39	28.7	1.89	0.59 NS
	Secondary school	4	5.9	6	8.8	10	7.4		
	Diploma	5	7.4	9	13.2	14	10.3		
Type of surgery	Plaque	3	4.4	4	5.9	7	5.2		
	Leg Reconstructive Surgery	1	1.5	1	1.5	2	1.5	12.11	0.43 NS
	Dynamic Hip Screw	8	11.8	16	23.5	24	17.8		
	Total Knee Arthroplasty	6	8.8	6	8.8	12	8.9		
	Orthopedic	43	63.2	38	55.9	81	60.0		

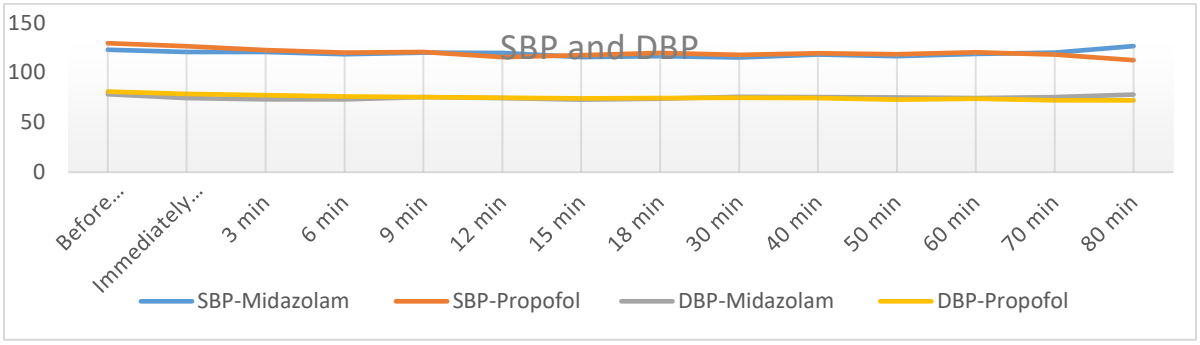
	Total Hip Replacement	2	2.9	0	0	2	1.5		
	Others	5	5.8	3	4.4	8	4.4		
Vomiting	Yes	4	5.9	4	5.9	8	5.9	>0.99	>0.99
	No	64	94.1	64	94.1	128	94.1		NS
Hypotension	Yes	8	11.8	9	13.2	17	12.5	0.06	0.79 NS
	No	60	88.2	59	86.8	119	87.5		
Transfusion	Yes	1	1.5	4	5.9	5	3.7	1.86	0.17 NS
	No	67	98.5	64	94.1	131	96.3		

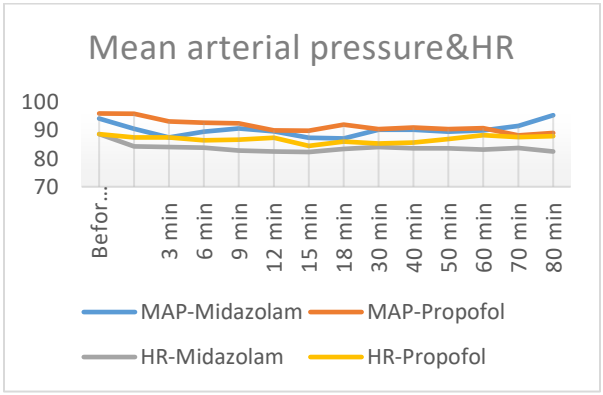
NS: Not significant

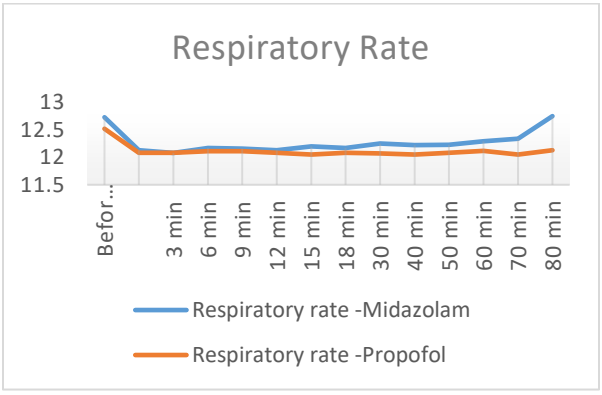
Table 2- Cognitive dysfunction features before and after anesthesia and surgery

Variables	Midazolam		Propofol		Total		Statistical test	P value
	Mean	SD	Mean	SD	Mean	SD		
Duration of cognitive dysfunction (days)	1.14	0.35	1.606	0.85	1.37	0.69	-3.52	*<0.005
Short-term memory before SA	3.69	1.341	3.63	1.42	3.66	1.37	-0.25	0.79
Long-term memory before SA	3.61	2.98	3.63	2.96	3.62	2.96	-0.21	0.82
Preoperative cognitive dysfunction	73.08	12.48	73.21	12.18	73.15	12.2	-0.05	0.95
Short-term memory after SA	3.92	1.49	4.13	1.46	4.02	1.48	-0.65	0.51
Long-term memory after SA	3.75	2.88	4.25	3.12	4	3.00	-0.88	0.37
Postoperative cognitive dysfunction	75.61	12.22	77.34	12.67	76.48	12.43	0.607	0.54

SA: spinal anesthesia *: significant







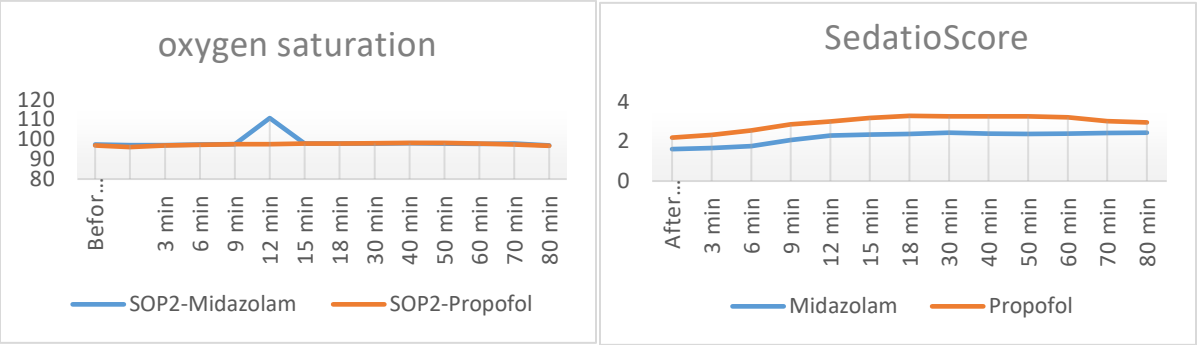


Figure 2- SBP, DBP, MAP, HR, RR, SPO2 and sedation Changes in different times

Table 3- Mean onset and recovery time of sedation, and anesthesia &surgery duration

Variables (Min)	Midazolam		Propofol		Total		Statistical test	P value
	Mean	SD	Mean	SD	Mean	SD		
Onset time of sedation	5	0	1.13	0.69	3.08	2	-11.11	<0.005*
recovery of sedation	39.19	3.41	29.46	3.54	34.43	5.98	-10.56	<0.005*
Anesthesia duration	91.57	29.16	86.39	20.54	88.98	25.26	-0.78	0.97
Surgery duration	74.92	28.07	73.22	19.81	74.07	24.22	-0.03	0.433

*: significant

Table 4- Comparison of Midazolam and Propofol before and after operation regarding WMS-III categories

	Before operation						After operation					
	Midazolam		Propofol			P	Midazolam		Propofol			P
	Mean	SD	Mean	SD	Z	value	Mean	SD	Mean	SD	Z	value
Spatial addition	3.72	1.36	3.61	1.38	0.22	0.63 NS	4.801	7.37	4.14	1.44	-0.55	0.58 NS
Navigation	4.02	1.31	4.25	0.85	0.93	0.76 NS	4.206	1.27	4.45	0.88	-0.76	0.44 NS
Mental control	2.94	2.31	3.41	2.23	1.25	0.26 NS	3.44	2.37	4.07	2.24	-1.53	0.12 NS
Logical memory	2.94	2.13	2.49	2.21	2.23	0.13 NS	3.44	2.03	3.404	2.38	-0.51	0.606 NS
Repetition	3.61	2.98	3.59	2.99	0.06	0.803 NS	25.48	12.26	26.58	18.55	-0.88	0.37 NS
Visual reproduction	2.36	2.79	2.806	2.908	0.75	0.38 NS	3.75	2.88	4.25	3.12	-0.84	0.4 NS
Verbal paired associates	5.66	3.49	5.09	3.86	1.04	0.307 NS	2.603	2.87	3.16	3.21	-0.58	0.55 NS
Total	25.48	12.26	26.58	18.55	0.04	0.83 NS	6.301	3.57	6.09	3.93	-0.71	0.47 NS

NS: Not significant

Discussion

In summary, our results showedno significant difference between the Midazolam and Propofol groups in terms of memory coefficients and cognitive dysfunction before and after spinal anesthesia. However, the sedative score was lower in the Midazolam group, compared to the Propofol group before anesthesia and at different times after anesthesia. Furthermore, the time of the onset of sedation and time of recovery from sedation were longer in the Midazolam group, compared to the Propofol group. A negative correlation was found between memory coefficient and age; however, memory coefficient was not correlated with gender and anesthesia duration.

The possible effects of anesthesia medications on the short and long-term memory system arethe main concern of health professionals, especially among elderly patients. The reported incidence of POCD after major surgeries is different based on the sample size characteristics and conditions, such as the definition of POCD and the timing of the testing. The incidence of POCD three months after surgery was reported to be between 8%and 17% in the previous studies [12-14]. The

POCD is associated with poor functional recovery, increased length of hospital stay, and increased costs [15].

Based on some animal studies, anesthesia with Propofol does not affect the cognitive dysfunction in rats [16-17]. On the other hand, another animal study showed that the use of sedation with Propofol and Midazolam was associated with learning and cognitive dysfunction on the first day, compared to the control group, which was decreased in the Propofol group in the following days; however, it was not observed in the Midazolam group [18]. Limited human studies have assessed the incidence of cognitive decline before and after anesthesia with Midazolam or Propofol agents. The incidence of delirium and POCD due to the use of Midazolam, especially in elderly patients is reported in some studies [19-20], while there is evidence on the decreasing delirium in elderly patients undergoing hip fracture repair under spinal anesthesia with Propofol sedation [19]. Shao indicates that anesthetic Propofol could improve cognitive function in elderly and Alzheimer's disease patients [21]. A higher quality of sedation in terms of neuropsychometric recovery and patient tolerance for Propofol, compared to Midazolam, has been reported byClark et al. [22]. On the other hand, another study reported the same degree of memory impairment due to the use of Propofol at equal sedation as Midazolam [23].

Similar to our study, the effects of Propofol, Dexmedetomidine, and Midazolam on POCD in elderly patients were assessed in one study by Li et al. The least impact on cognitive function one week after the operation was observed in the Propofol group, while Midazolam tended to impair cognitive function. They suggested Propofol as viable sedation in patients with concentration, attention, and executive dysfunction problems. Furthermore, information processing problem, language impairment, and executive dysfunction were reported in patients who underwent Midazolam spinal anesthesia, compared to those received Propofol [24]. Wilson et al. assessed the effects of Propofol and Midazolam on patients undergoing orthopedic surgery under spinal anesthesia. They reported a higher mental function restoration following Propofol administration, compared to Midazolam; in addition, amnesia was greater immediately after the operation in the Midazolam group [25]. However, no difference was found between Propofol and Midazolam in any categories of cognitive dysfunction and memory coefficient. The discrepancies may be due to differences in the timing of the testing, and the instruments used to assesscognitive and memory problems. Although Li et al. found a difference in terms of cognitive dysfunction after the operation, they found no difference regarding cognitive dysfunction in elderly patients receiving Midazolam and Propofol one year after operation [24]. Another study showed that Midazolam administration led to increasing the risk of POCD in elderly patients [26].

Another similar study performed by Bhosale et al. investigated 60 patients under spinal anesthesia in two groups of sedation with Propofol (0.5 mg/kg) and Midazolam (0.02 mg/kg). The results showed that the mean duration lengths of sedation for Midazolam and Propofol were 10 and 9 min, respectively. Moreover, the mean recovery times from sedation for Midazolam and Propofol were 18.17 and10.40 min, respectively. They concluded that Propofol should be preferred during spinal anesthesia due to its rapid onset of action, better recovery, and fewer side effects [27]. Similarly, our findings showed that the time of onset of sedation and time of recovery from sedation were lower in the Propofol groups, compared to the Midazolam groups.

Based on Sieber et al., studies limiting the level of sedation can be effective in reducing postoperative delirium incidence by up to 50% [6, 28]. Konishi et al. compared the elderly patients who received Sevoflurane or Propofol following the administration of a spinal anesthetic regarding the incidence of POCD. The results showed that the incidence of POCD was not influenced by the type of anesthesia [29]. Similar to our study, Sarasiet al. showed that there was no significant difference between Propofol and Midazolam in terms of cognitive dysfunction.They indicated that the agents produced equivalent impairments [30]. According to a study conducted by Padmanabhan et al., the addition of Midazolam 2 mg (0.5-10) to Propofol sedation did not lead to more cognitive dysfunction, compared to the use of Propofol alone [31]. Based on other studies, there was no statistically significant difference between Propofol and Midazolam in terms of patient satisfaction, duration of recovery, injection pain, and other complications [32-33].

In general, there are conflicting data regarding the effects of Midazolam and Propofol on cognitive problems in elderly people undergoing spinal anesthesia. Cognition status is evaluated within the first week after surgery in some studies, while the assessment of patients at this time interval is complicated because of residual anesthetic agents and the stress of operation. On the other hand, the cognitive change associated with anesthesia and surgery should not be classified as neurocognitive dysfunction in the stage. However, it should be labeled as delayed neurocognitive recovery, which emphasizes the transient of the changes [34]. Based on the aforementioned data, further studies are recommended to be conducted in this regard to check our findings and achieve reliable data.

Limitations

This study did not assess the effect of pain and anxiety on the level of memory and cognitive function before and after anesthesia, which was one of the most important

limitations of our study that might have affected the results. Moreover, the memory condition and cognitive function of the patients were not evaluated at the follow-up. Therefore, it is suggested that future studies assess the long-term effect of spinal anesthesia on memory and cognitive functions.

Conclusion

In summary, no difference was found between the Midazolam and Propofol groups in terms of memory function and cognitive dysfunction before and after spinal anesthesia, which revealed that these agents did not affect the memory coefficient or cognitive dysfunction. However, the sedative score was lower in the Midazolam group, compared to the Propofol group. Moreover, the onset time of sedation and time of recovery were longer in the Midazolam group, compared to the Propofol group.

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