Original Article

Effect of Midazolam on Immediate Cognitive Function during Total Intravenous Anesthesia in Elderly Hepatocellular Carcinoma Patients Undergoing Radiofrequency Ablation

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Background: Previous studies showed that midazolam had some effects on cognitive dysfunction.

Objective: To study the drug effects by using the Montreal Cognitive Assessment Test to assess cognitive function in the elderly with hepatocellular carcinoma during total intravenous anesthesia (TIVA) after radiofrequency ablation (RFA).

Materials and Methods: Ninety geriatric patients, aged 65 to 80 scheduling for RFA under TIVA were randomized into two groups, A (n=51) receiving midazolam and B (n=39) without midazolam. Prior to the procedure, the first Montreal Cognitive Assessment Test was done. The second test was done when the patients gained full-conscious in the recovery room.

Results: The pre-test and post-test scores were comparable between the two groups. Interestingly, the participants in group A and B had normal scores prior to starting the anesthesia and the score decreased after the surgical procedure. Fifty-one and thirty-four patients, with and without midazolam showed the incidence of cognitive dysfunction as 33.3% and 14.7%, respectively. The score in group A appeared to decrease significantly ($p<0.01$) after the operation. This was not observed in group B.

Conclusion: Under TIVA with midazolam, 60% of the elderly with hepatocellular carcinoma after RFA showed a significant decrease of immediate cognitive function.

Keywords: Elderly, Midazolam, Montreal Cognitive Assessment Test, Radiofrequency ablation.

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Annually, the department of Anesthesiology serves 50,000 patients for both general and regional anesthesia such as orthopedic, eye, ear, nose and throat, neurological, cardiovascular, dental, plastic, pediatric, general, urology, head neck and breast, obstetrics and gynecology, and trauma surgeries as well as radiology, acute pain, and intensive care unit.

Normally, a radiologist uses thermal effect at 90°C to 100°C emitted from radiofrequency ablation (RFA) needle to destroy hepatocellular carcinoma and its surrounding tissue at a distance of 2 to 5 centimeters. By this means, it results in mild postoperative pain to most surgical patients[1].

Currently, total intravenous anesthesia (TIVA) is a technique of choice in patients undergoing RFA. The anesthetics including propofol, fentanyl or midazolam are used to provide rapid, precise hypnosis, analgesia, and amnesia. Consequently, TIVA yields a conscious sedation with the facility to secure airway, a slight response to noxious stimuli with procedural pain suppression[2]. However, previous studies showed that midazolam had some effects on the elderly regarding memory, thought, learning, verbal ability, perception, olfactory function, attention, information processing, executive function, abstract thinking, and concentration[3]. These postoperative cognitive dysfunctions can be confirmed by the special neuropsychological tests[3-5].

There were 127 and 120 geriatrics out of 288 and 366 patients that underwent total TIVA for RFA

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in 2015 and 2016, respectively.

The Montreal Cognitive Assessment (MoCA) is a bedside, practical screening tool for cognitive assessment. It can detect various functions such as intention, concentration, memory management, visual relationship skills, and modeling. The cut-off score 26 of the full score 30 is considered normal[6-8]. The MoCA has been used worldwide in many fields[9].

The objective was to study the effect of midazolam, by using the MoCA to assess cognitive function in the elderly with hepatocellular carcinoma during TIVA after RFA.

Materials and Methods

The present study was a prospective cohort study approved by the Siriraj Institutional Review Board (COA: Si164/2018), registered via Thai Clinical Trial Registry (TCTR20180913004), and written inform consents were obtained from all subjects.

Since patients without and with midazolam had effect on cognitive function as 6.8%[4,11] and 40%[5,8] by inductive inference or observation, the calculated population was equal to 34 over 0.4 or 85. Five percent was added for drop out purpose. Therefore, ninety patients were enrolled in the present study between May 1, 2018 and February 1, 2019.

The inclusion criteria were male and female patients, aged 65 to 80, American Society of Anesthesiology (ASA) I to III, known case of hepatocellular carcinoma, educational level above sixth grade, with ability in listening, speaking, reading, and writing.

The exclusion criteria were preoperative neurological deficit such as Parkinson's disease, dementia, cerebrovascular disease, alcoholism, poor activity of daily rounds, malnutrition, hearing or vision defects, dehydration, electrolyte imbalance, insomnia, on Foley's catheter, disorder of intellectual, acute confusion, hypoxia, hypoxemia and decreased level of hemoglobin, narcotic and benzodiazepine administration, and postoperative pain score greater than 3. Patients unwilling to continue the study could withdraw at any time.

Prior to the procedure, the investigator invited the scheduled patients for RFA to join the study. Then the first MoCA was evaluated by a co-research.

On the day of surgery, patient was monitored with oxygen saturation, pulse rate, and blood pressure, under the supervision of an anesthesiologist and both groups were administered fentanyl 1 to 2 mcg/kg and bolus dose of propofol 0.5 to 1 mg/kg followed by 4 to 12 mg/kg/hour drip intravenously via syringe pump while group A was administered midazolam 0.1 to 0.2 mg/kg intravenously during anesthesia. There were fifty-one and thirty-nine patients in group A and group B, with and without midazolam, respectively. After the procedure, the patients were referred to the recovery room. The postoperative pain score and second MoCA test were assessed when the patients regained full consciousness in the recovery room. The investigator performed all MoCA test without knowing whether any midazolam was administered during anesthesia.

Statistical analysis

The data was expressed as percentage, mean and standard deviation. Categorical data were compared by chi-square test. Fisher's exact test was used to compare the pre and post cognitive score between the two groups. A p-value of less than 0.01 was considered as statistically significant difference at the 95% confidence interval.

Results

Five patients in group B were excluded during the study due to hyperpyrexia (2), enlarged tumor mass (2) and brain metastasis (1). Thus, fifty-one (A) and thirty-four (B) patients completed the study. The demographic data including gender, age, body mass index (BMI), ASA classification, education, pain score and duration of the procedure showed no differences between the two groups (Table 1).

Fifty-one and thirty-four patients with and without midazolam showed the incidence of cognitive dysfunction as 17 (33.3%) and five (14.7%) patients, respectively (Table 2).

The pre-test and post-test MoCA scores were comparable between the two groups. Interestingly, the participants in group A and B had normal MoCA scores prior to anesthesia and showed to decrease after the surgical procedure. The MoCA score in group A appeared to decrease significantly ($p<0.01$) after the operation, which was not observed in group B (Table 2).

Discussion

Cognitive impairment is rapidly increasing its prevalence with ageing population and becomes an important public health concern in developed and developing countries[10]. Fifty-one, elderly patients (60%) underwent RFA under TIVA with midazolam and showed significant decrease in cognitive function. The reasons for this adverse event had many aspects.

Firstly, midazolam easily affects cognitive

Table 1. Demographic characteristics

	Midazolam (n=51); n (%)	Non-midazolam (n=34); n (%)	p-value
Age (year); mean±SD	70±4.5	73±4.4	0.434
Sex: male:female	35:16	23:11	
Weight (kg); mean±SD	68±11.8	63±10.3	
Height (cm); mean±SD	163±6.6	161±7.6	
BMI (kg/m^2); mean±SD	25.7±4.4	24.5±3.9	0.379
Education (years) (<12:>12)	51:49	73:27	
ASA physical status			
I	0 (0)	0 (0)	
II	27 (53)	19 (56)	
III	24 (47)	15 (44)	
Duration (minute); mean±SD	141.4±49.7	141.2 ±32.8	0.984
Pre-anesthetic problems	45 (88.2)	29 (85.3)	
Hypertension	35 (68.6)	24 (70.6)	
Diabetes mellitus	15 (29.4)	11 (32.4)	
Cardiovascular disease	4 (7.8)	2 (5.9)	
Kidney disease	7 (13.7)	6 (17.6)	
Pain score			0.440
0	38 (75.0)	24 (71.0)	
1	11 (22.0)	9 (27.0)	
2	2 (4.0)	0 (0.0)	
3	0 (0.0)	1 (3.0)	

BMI=body mass index; ASA=American Society of Anesthesiology; SD=standard deviation

p<0.01 significant

Table 2. Montreal Cognitive Assessment in elderly hepatocellular carcinoma patients undergoing radiofrequency ablation

	Midazolam (n=51); n (%)	Non-midazolam (n=34); n (%)	p-value
Cognitive dysfunction	17 (33.3)	5 (14.7)	
Pre-test; mean±SD	28.0±1.2	27.4±1.1	0.802
Post-test; mean±SD	26.5±1.5	26.9±1.4	0.271
p-value	0.000*	0.018	

SD=standard deviation

p<0.01 significant

function in the elderly since the cerebral circulation is distorted in patients in the higher age group[11]. In addition, the drug acts at the gamma-aminobutyric acid (GABA) receptor in the nervous system with rapid onset and clearance. Its imidazole ring, a fat-soluble, would easily pass through the blood brain barrier[12]. This was consistent with Hsu et al in a prospective case-controlled study on evident cognitive impairments in seemingly recovered patients after midazolam-based light sedation during diagnostic endoscopy. They claimed that low-dose midazolam could prolong cognitive impairment[13]. Hong et al in a study regarding the effect of midazolam upon memory during fiberoptic gastroscopy under conscious sedation, revealed that the drug could cause transient selective anterograde amnesia in a dose-dependent manner[14]. However, Ulusoy et al and Mansouri et al in their double-blind studies showed that midazolam did not reduce postoperative cognitive dysfunction significantly[15,16].

Secondly, midazolam lengthens its efficacy in the elderly since the drug excretion is impaired in patients with advanced age[17]. An elimination half-life of midazolam and its active metabolites is prolonged as age-related organs dysfunction. In addition, drug metabolism via renal and liver function (cytochrome P450) is compromised as vascular walls become thicker and more rigid in ageing[17]. This was supported by Kinirons et al in an article on drug metabolism and ageing. They found that the increasing inter-individual variability in drug metabolism, drug action and adverse reactions was a feature of advancing age. Changes in drug disposition with ageing could be inferred as being due to changes in conventional physiological changes[18]. Shi et al in the study on age-related changes in pharmacokinetics revealed that ageing was characterized by a progressive decline in the functional reserve of multiple organs and systems, which could influence drug disposition. In addition, co-morbidity and poly-pharmacy were highly prevalent in the elderly[19].

Thirdly, as a number of nerve cells decrease in elderly, midazolam can exacerbate its response by the decline of cognitive function[11]. Age-related decreases in the expression of brain-derived neurotrophic factor in the hippocampus have been reported[12] and might contribute to age-related cognitive impairment[11]. This agreed with Hou et al in the study on ageing as a risk factor for neurodegenerative diseases[20]. In addition, Mattson et al in the study on ageing and neuronal vulnerability believed that these were unavoidable changes that occur during normal ageing or the prodromal to a fatal neurodegenerative disorder, increases in oxidative stress and DNA damage[21]. However, it was conceivable that the initiation of nerve cell death was programmed to occur after a given period, independently of the cell modifications caused by ageing[21].

And finally, patients' educational level is expected to comprehend in performing the MoCA test since those with less educated may lack experience in dealing with complex problem solving.

In addition, a cognitive impairment is higher in accordance with didactic level. Studies showed that an education of less than nine years had a slight rate of cognitive deficiency compared to those studied more than 13 years[22]. As a result, the sixth grade of learning level was determined as cut-off point for all participants to follow the test thoroughly[6,23]. This was consistent with Deetong et al in the study on the prevalence and risk factors of mild cognitive impairment in menopausal women. During a face-to-face interview of patient participating in the MoCA, they found that the significant associated risk factors were low education[23]. In addition, this agreed with Vichitvejpaisal et al in the study on the MoCA as a screening tool for preoperative cognitive impairment in geriatric patients. They concluded that education correlated positively and sharply with the score[6].

However, Van Gerven et al found that high educational attainment might be a risk factor for accelerated cognitive decline in older age and cognitive reserve framework[24]. Yet, education did not have significant protective power against age-related cognitive decline. Additionally, Zahodne et al believed that years of education did not appear to moderate cognitive trajectories[25].

Conclusion

Under TIVA with midazolam, 60% of the elderly with hepatocellular carcinoma after RFA showed a significant decrease of immediate cognitive function under TIVA.

What is already known on this topic?

Currently, most radiofrequency ablation procedure has been performed under total intravenous anesthesia. The anesthetics are propofol, fentanyl or midazolam. However, previous studies showed that midazolam had detrimental effects on immediate cognitive function in the elderly.

What this study adds?

MoCA is a bedside, practical screening tool for cognitive assessment. Investigators found that it could help to assess cognitive function in the elderly with hepatocellular carcinoma after the surgical procedure.

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Conflicts of interest

The authors declare no conflict of interest.

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