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Original Article

The effect of midazolam on delirium in patients undergoing coronary artery bypass surgery

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Abstract

Aim: Delirium is a serious complication seen postoperatively in patients undergoing cardiovascular surgery. In this study, we aimed to investigate the effect of midazolam given preoperatively on the incidence of delirium in the postoperative period in patients undergoing open heart surgery.

Material and Methods: The files of patients who underwent open heart surgery between 2017-2019 in Cardiovascular Surgery Intensive Care Unit were retrospectively reviewed. 50 patients were included in the study. Ramsey Agitation Sedation Scale (RASS) and Confusion Assessment Method (CAM-ICU) values were recorded preoperatively, before and after extubation, in the ICU (after the first 24 hours) and after service transfers. Patients were divided into two groups as midazolam used or midazolam-free.

Results: 28 patients were male (56%) and 22 were female (44%). The rate of delirium before extubation (T0) during the ICU stay period was significantly higher in the group without midazolam (p = 0.01). Similarly, the rate of delirium after extubation (T1) was found to be high in the group without midazolam (p = 0.00). There were also significant differences in extubation times. It was found 5.48 ± 1.08 hours in the group using midazolam and 8.3 ± 0.69 hours in the group without midazolam (p = 0.00).

Conclusion: The use of midazolam in induction and perfusion in patients undergoing cardiopulmonary bypass could reduce the development of delirium in the postoperative period. Besides, RASS and CAM-ICU evaluation forms could be useful in early detection and monitoring of postoperative delirium.

Keywords: Midazolam; cardiopulmonary bypass; delirium

INTRODUCTION

Delirium is an acute brain disease with changes in consciousness, attention, informatics and perception. It is one of the most common neurologic complications seen in all intensive care units, especially after open heart surgery (1). Worldwide, more than 2 million cardiac surgery operations are performed annually. Although the mortality rates have decreased with the development of techniques in cardiac surgery, the incidence of major complications are still between 14.4% and 30.1%. These complications significantly increase the length of hospital stay and cost (2).

Delirium is characterized by sudden onset and fluctuating mental status, disorganized thinking, and change in consciousness (3) and can cause rapid deterioration in cognitive functions, re-hospitalization and increase in mortality rates. The incidence of delirium in cardiac surgery is 11-46%. Delirium can be prevented by 30-40% (4). Some of the modifiable risk factors are analgesic and sedative agent choices (5). Many factors such as male sex, alcohol habit, dehydration, multiple drug use, pain, neuroleptic and narcotic use may induce delirium. Severe disease status, initially cognitive dysfunction and advanced age are the most important factors increasing the incidence (6).

It has been stated that the delirium cannot be adequately diagnosed, although it has been shown to be widespread and important by numerous epidemiological studies (7).

It has been reported that 64-84% of patients with delirium have not been noticed and 33-66% have not been diagnosed (8,9). Various tests and scales are used for delirium evaluation. Confusion Assessment Method (CAM-ICU) is one of the most frequently used scales for the diagnosis of delirium in intensive care unit (10).

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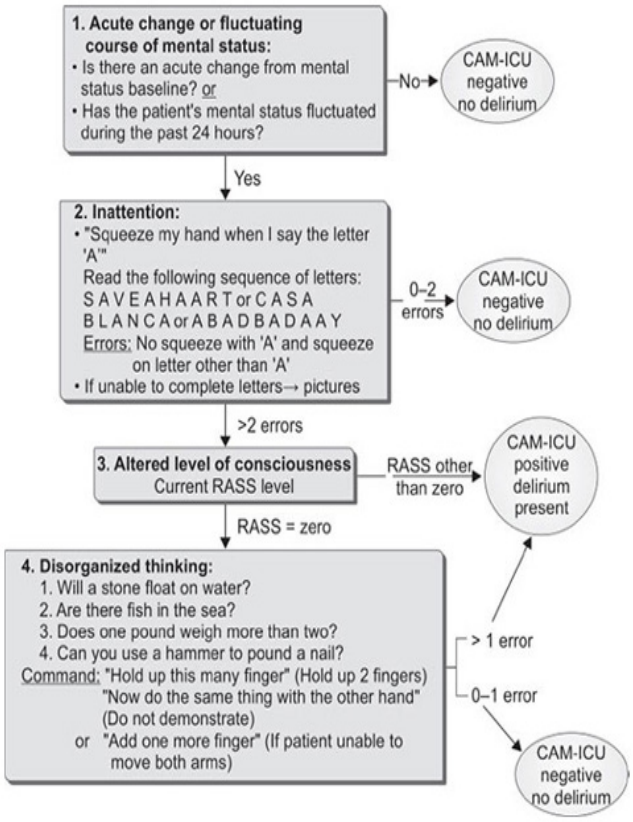
In this study, we investigated the incidence of postoperative delirium in cardiopulmonary bypass patients with and without midazolam use between 2017 and 2019. This study was approved by the Ethics Committee of Harran University (ID: 09/10/30) on 09 September 2019.

MATERIAL and METHODS

The files of the patients who underwent cardiac surgery applying cardiopulmonary bypass procedure were performed retrospectively from the hospital records and hospital information processing system between 2017-2019. Demographic data, anesthesia techniques, ventilation management, drugs used in induction and maintenance of anesthesia (intravenous, inhalation agents, neuromuscular blocker), intraoperative complications, other drugs used during anesthesia (reversal agents, steroids, etc.) hospitalization times, ICU stay time, ejection fractions (EF), extubation times, cross-clamp times, total cardiopulmonary bypass times, Confusion Assessment Scale (CAM-ICU) and Ramsey Agitation and Sedation Scale (RASS) scores (Table-1 and Figure-1) are recorded (11). The diagnosis of delirium was determined according to the data on the scales. Patients with a score of 4 or less in RASS who underwent CAM-ICU were evaluated. Patients identified as negative on CAM-ICU were considered to have no delirium. Delirium was diagnosed in patients who were considered positive on CAM-ICU. Details of both scales are shown in Table 1 and Figure 1 (11).

Table 1. Richmond Agitasyon Sedation Scale (RASS)

+4 Combative Overtly combative, violent, immediate danger to staff
+3 Very agitated Pulls or removes tube(s) or catheter(s); aggressive
+2 Agitated Frequent non-purposeful movement, fights ventilator
+1 Restless Anxious but movements not aggressive vigorous
0 Alert and calm
-1 Drowsy Not fully alert, but has sustained awakening (eye-opening/ eye contact) to voice (>10 seconds)
-2 Light sedation Briefly awakens with eye contact to voice
-3 Moderate sedation Movement or eye opening to voice (but no eye contact)
-4 Deep sedation No response to voice, but movement or eye opening to physical stimulation
-5 Unarousable No response to voice or physical stimulation



Patients with delirium will display changes from their mental status baseline and/or fluctuation in mental status. Feature 1 assesses for these changes. In Feature 2, alertness is a basic arousal process in which the awake patient can respond to any stimulus in the environment. The alert, but inattentive patient will respond to any sound, movement, or event occurring in the vicinity, while the attentive patient can screen out irrelevant stimuli. All attentive patients are alert, but not all alert patients are attentive. Patients with delirium experience a disturbance of consciousness and changes in cognition. For the CAM-ICU this is measured by using the RASS scale and assessing current level of consciousness. If Features 1 & 2 are absent, you do not need to proceed with Feature 3. This is the hardest area to assess in nonverbal patients because it is the most subjective of the four Features. Thought is expressed by verbal or written words. Mechanical ventilation and loss of fine motor movement limit this expressive ability in most ICU patients. Because of this, the CAM-ICU uses easy questions and a simple 2-step command to assess organization of thought. If Features 1 & 2 are absent, you do not need to proceed with Feature 4 (11).

Figure1. Confusion Assessment Method (CAM-ICU)

Postoperative heart or respiratory failure (COPD, heart failure, pulmonary embolism and similar), patients who need mechanical ventilation and patients with sedation scores of 5 and 6 were excluded. In addition, patients with low ejection fraction (EF <30), patients with long cross-clamp time (> 60 min.), patients with longer total cardiopulmonary bypass time (CPB) (> 120 min.), patients under 18 years, chronic renal failure, chronic obstructive lung disease, liver dysfunction, emergency patients and additional medication during induction were excluded. After exclusion, 50 patients were included in the final. The patients were divided into two groups. It was recorded that propofol 1-2 mg / kg, fentanyl 1 microgram / kg and

esmeron 0.6 mg / kg were given to both groups in induction and fentanyl and esmeron were given intraoperatively. The total dosage of midazolam was up to 15 mg at maximum depending on the patients' weight. The control group was selected from patients who did not receive midazolam during anesthesia induction and CPB. The second group consisted of patients who received 0.1 mg / kg midazolam during anesthesia induction and CPB. CAM-ICU and RASS datas were recorded before extubation (T0), after extubation (T1) and after intensive care unit (T2). Patients with and without delirium were identified in the groups. Statistical analyzes were performed and compared.

Statistical Analysis

For statistical analysis and calculations, IBM SPSS Statistics 23.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA) was used. Data are presented as mean ± standard deviation, n (%). Percentage, chi-square, Fischer, and Mann-Whitney U tests were used for data analysis. Statistical significance level was accepted as p <0.05.

RESULTS

The demographic information of the patients and the characteristics of the operations performed are summarized in Table 2. 22 patients were female (44%) and 28 were male (56%). The incidence of delirium in patients older than 65 years was found to be 45%. In the analysis of demographic data, there was no significant statistical difference between the groups in terms of delirium development. However, extubation times, pre-extubation and post-extubation ICU follow-up showed significant differences between the groups.

Mean extubation time was found to be 5,48±1,08 hours in the midazolam group and 8,3 ±0,69 hours in midazolam-free group (p=0,00). Intensive care stay was significantly different between the two groups. The duration of ICU stay was short in the midazolam group (p<0,05) (Table 3). The rate of delirium seen in the intensive care unit before extubation (T0) was 32% (n=8) in the group receiving midazolam and 80% (n = 20) in the midazolam-free group. (p=0,01). The rate of delirium seen in the intensive care unit after extubation (T1) was 28% (n=7) in the midazolam group and and 80% (n = 80) in the midazolam-free group (p=0,00) (Table 3). There was no significant difference between the groups in the follow-up (T3) of the patients.

Table 2. General characteristics of patients

Age (Years)	*56±3.29*
Male [n (%)]	28 (%56)
Female [n (%)]	22 (%44)
Ejection Fraction (%)	48.96±5.48
CCT (min)	47.85±34.1
CPBT (min)	103.6±15.9
ICU stay (day)	3.86±1.22
Hospital stay (day)	9.68±1.83
Extubation Time (hour)	6.92±1.70

CCT: Cross Clamp Time, CPBT: Cardiopulmonary Bypass time
ICU: Intensive Care Unit

Table 3. Statistical occurrence of delirium between groups.

	MİDAZOLAM pozitive (n=25)			MİDAZOLAM negative (n=25)		
	Delirium posititive (n=8)	**Delirium negative (n=17)**		**Delirium positive (n=20)**	**Delirium negative (n=5)**	
T0	8 (%32)	17 (%68)	T0	20 (%80)	5 (%20)	**P=0,01**
T1	7 (%28)	18 (%72)	T1	20(%80)	5 (%20)	**P=0,00**
T2	1(%4)	24(%96)	T2	1(%4)	24(%96)	P=0.77
Male [n (%)]	4(%50)	10(%58.8)		14(%70)	0(%0)	P=0.1
Female [n (%)]	4(%50)	7(%41.2)		6(%30)	5(%100)	P=0.8
Extubation Time(hour)	5.88±1.33	5.29±0.92		8.45±0.65	8.0±0.79	**P=0.00**
ICU stay time (day)	3.88±0.35	2.41±0.51		4.90±0.64	4.60±0.55	**P=0.00**
Hospital stay Time (day)	11.63±1.30	8.70±1.49		9.60±1.81	10.2±1.3	P=0.81

CCT: Cross Clamp Time, CPBT: Cardiopulmonary Bypass time
IT0: Before Extubation T1: After Extubation T2: After ICU stay

DISCUSSION

It is very difficult to communicate with patients in the intensive care unit. Therefore, it can be difficult to detect and diagnose delirium in critically ill patients. Diagnosis of delirium in patients undergoing mechanical ventilation, a Confusion Assessment Scale (Confusion Assessment Method for The Intensive Care Unit; CAM-ICU), which can be used by non-psychiatrists such as nurses and intensive care physicians has been developed. CAM-ICU was developed by Inouye for the evaluation of delirium by neuropsychiatrists based on the definition of delirium in the American Psychiatric Association's Diagnostic and Statistical Manual-DSMIV. CAM-ICU evaluates (a) acute onset or fluctuations of mental status, (b) lack of attention, (c) disruption of thinking, and (d) change of consciousness; it has been reported that it is easy and reliable to use in patients who cannot communicate verbally and / or are connected to ventilator (12). The patient's assessment is initiated using the Richmond Agitation and Sedation Scale (RASS) and CAM-ICU. Original validity study of CAM-ICU was found to be high in sensitivity (95%) and specificity (98%). The advantage of using CAM-ICU is that it allows being evaluated patient in as little as 2-5 minutes on average and is very reliable in evaluation. Another advantage of CAM-ICU is that it is not dependent on the patient's speech when performing delirium evaluation. For this reason, CAM-ICU also enables the evaluation of patients who cannot express themselves orally or intubated.

Midazolam is a benzodiazepine containing imidazole group. It is water soluble and short-acting (half-life 1,5 - 3 hours). Depending on the dose, it has anxiolytic and then sedative, hypnotic and retrograde amnesic effects. Like other benzodiazepines, it binds to gamma-amino bituric acid (GABA) -A receptors in the central nervous system and increases the activity of the inhibitor neurotansmitter GABA (13). Reduces dopaminergic neuronal activity and 5-HT release by binding to the GABA complex (14). It blocks brain stem and reticular system activity in EEG. Antegrade provides amnesia when given intravenously, but this effect is short-lived. Depending on the dose, there is a wide range of effect from mild sedation to general anesthesia. The anxiolytic effect of midazolam has been demonstrated in several double-blind placebo-controlled studies (15).

Preoperative and postoperative use of benzodiazepine has been reported to be related to the incidence of delirium (16,17). It has been reported that patients receiving benzodiazepines for premedication entered the delirium 2.39 times more than patients not receiving benzodiazepines (4). Lin YY et al. suggested that sedatives such as midazolam secreted mediators that cause delirium by acting through GABA receptors (18). Cui Y. et al reported that there was a relationship between the use of midazolam and the depth of sedation and that deep sedation may cause impairment of cognitive functions (19). In the examination of delirium tables developed after medical applications in cardiac surgery, delirium increased by 7-8% with 1 mg midazolam after cardiac surgery (20).

Midazolam is used as a routine premedication in patients who underwent surgery all over the world. It is generally applied to relieve preoperative anxiety, sedation induction, to decrease intraoperative awareness and to provide hemodynamic stability (21). In the literature, there is not enough study about the extent of postoperative use of benzodiazepines which may be preferred in cardiac surgery due to their hemodynamic profiles and amnestic properties affecting the incidence of delirium in the postoperative period (22). Studies have suggested that preoperative and postoperative benzodiazepine use is associated with an increased risk of delirium and therefore it has become common practice to minimize perioperative benzodiazepine use to prevent postoperative delirium (16). However, these studies are generally in the form of a comparison of dexmedetomidine and benzodiazepines (23). When dexmetedomin is compared with propofol, dexmetedomin has been shown to cause less delirium and reduce extubation times in cardiac surgery (2). Similarly, comparing dexmetedomin with morphine and midazolam, there was no difference in delirium formation rates between drugs (24).

Sevoflurane, midazolam and propofol were compared and NIRS was followed by tissue oxygen saturation in the brain during cardiopulmonary bypass. It was reported that postoperative neurocognitive functions did not change with all three anesthetic agents (25). There are some studies that suggest that benzodiazepine premedication is advantageous and prevents delirium, but these studies are still insufficient (26). Therefore, our study contributes to the literature in terms of showing that the use of midazolam before surgery provides a decrease on delirium in patients with open heart surgery.

CONCLUSION

The use of midazolam in patients undergoing cardiac surgery could reduce the delirium after the operation. In addition, the standard use of the confusion assessment method in postoperative cardiac surgical care could be useful for the rapid detection and treatment of delirium. Extensive prospective studies in the future will increase our knowledge on this subject.

Competing interests: The authors declare that they have no competing interest.

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