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Original Article / Özgün Makale

Postoperative delirium associated with prolonged decline in cognitive function and sleep disturbances after cardiac surgery

Kardiyak cerrahi sonrası uzayan kognitif fonksiyon kaybı ve uyku bozuklukları ile ilişkili ameliyat sonrası deliryum

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Background: This study aims to investigate the association between postoperative delirium and cognitive dysfunction after cardiac surgery and to determine the effects of postoperative delirium on postoperative cognitive dysfunction and sleep disturbances in the long-term.

Methods: Among 285 patients who underwent open cardiac surgery between May 2010 and July 2011, 51 patients who met the inclusion criteria were enrolled in the study. Twenty-six patients (group 1) who developed postoperative delirium were compared with 25 patients (group 2) without delirium. Cognitive function was assessed by mini-mental state examination (MMSE) test at pre-discharge, six and 12 months after surgery. Involving into the working life was questioned in both groups at the 12 months after surgery. Functional ability was assessed by the assistance need for instrumental activities of daily living (IADL), whereas sleep disturbances were assessed by the Pittsburgh sleep quality index (PSQI).

Results: Patients in group 1 had lower mean MMSE scores compared to patients in group 2 before hospital discharge (26.0 versus 28.6, p<0.001). The mean MMSE scores were significantly lower in group 1 at six and 12 months after surgery (26.7 versus 29.2 and 28.0 versus 29, p<0.001, respectively). Sleep disturbances were also significantly higher at 12 months after surgery in group 1, compared to group 2 (73.1% versus 32.0%, p<0.001).

Conclusion: Postoperative delirium after cardiac surgery is a risk factor for prolonged postoperative cognitive dysfunction. It is also associated with a significant decline in cognitive ability and sleep disturbances during the first year after cardiac surgery.

Key words: Cardiac surgery; cognitive dysfunction; delirium.

Amaç: Bu çalışmada ameliyat sonrası deliryum ve kognitif disfonksiyon arasındaki ilişki ve ameliyat sonrası deliryumun kardiyak cerrahi sonrası uzun dönemdeki kognitif fonksiyon ve uyku bozuklukları üzerine olan etkileri araştırıldı.

Çalışma planı: Mayıs 2010 - Temmuz 2011 tarihleri arasında kliniğimizde açık kalp ameliyatı geçiren 285 hastadan çalışma kriterlerine uyan toplam 51 ardışık hasta çalışmaya alındı. Çalışmada ameliyat sonrası deliryum tanısı konulan 26 hasta (grup 1), deliryum tanısı konulmayan 25 hasta (grup 2) ile karşılaştırıldı. Kognitif fonksiyon, hastane taburculuğu öncesinde ameliyat sonrası 6. ve 12. ayda standardize mini-mental durum muayenesi (MMSE) testi ile değerlendirildi. Her iki grubun ameliyat sonrası 12. ayda çalışma hayatına katılımları sorgulandı. Fonksiyonel becerileri enstrümental günlük yaşam aktiviteleri (EGYA) için yardım ihtiyacı ile değerlendirirken, uyku sorunları, Pittsburgh uyku kalite indeksi (PSQI) ile değerlendirildi.

Bulgular: Grup 1'deki hastaların ortalama MMSE skorları, grup 2'deki hastalara kıyasla, taburculuk öncesinde daha düşüktü (26.0 ile 28.6, p<0.001). Grup 1'de 6. ve 12. aylarda ortalama MMSE skorları anlamlı olarak daha düşük idi (sırasıyla, 26.7'ye karşılık 29.2 ve 28.0'a karşılık 29.9, p<0.001). Uyku sorunları, ameliyat sonrası 12. ayda grup 1'deki hastalarda, grup 2'ye kıyasla, daha fazla idi (%73.1'e karşılık %32.0, p<0.001).

Sonuç: Kalp cerrahisi sonrasında ameliyat sonrası deliryum geçirmek uzun süreli ameliyat sonrası kognitif disfonksiyon için bir risk faktörüdür. Ameliyat sonrası deliryum, cerrahi sonrası ilk yıl süresinde hem kognitif fonksiyonda anlamlı azalma hem de uyku bozuklukları ile ilişkilidir.

Anahtar sözcükler: Kardiyak cerrahi; kognitif fonksiyon bozukluğu; deliryum.

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Postoperative cognitive dysfunction (POCD) is a common and well-known complication after cardiac surgery, with an incidence rate of between 25-80% in the early period and 10-60% after six months. It is characterized by a decline in cognitive function and impairment in life. Due to the characteristics of POCD, many physicians fail to notice the disturbances in patients' cognitive dysfunction after cardiac surgery. Even the patients themselves and their families may be unaware of the cognitive decline. Age is a major risk factor for POCD along with hypertension and diabetes mellitus (DM). Although a large proportion of patients return to their preoperative level of cognitive function within three months after surgery, POCD can be persistent, with lingering impairment or diminished quality of life the year after surgery.[1-4]

Postoperative cognitive dysfunction and postoperative delirium (POD) are frequently mistaken for each other. Contrary to POCD, POD is characterized by impairment of consciousness and attention. It is clinically defined as an acute confusional state characterized by disorientation, a disturbed sleep-wake cycle, memory impairment, perceptual disturbances, and altered psychomotor activity and is associated with adverse outcomes, including increased early hospital morbidity and mortality, increased healthcare costs, and functional and cognitive decline.[5] Although POD usually resolves within three days of initial hospitalization, in some cases, it may result in long-term functional and cognitive decline.[6,7] We followed up patients both with and without delirium for one year after cardiac surgery and examined the effects of postoperative delirium on their cognitive performance. Afterwards, we hypothesized that patients diagnosed as having POD are more prone to POCD in the long-term.

The aim of this study was to investigate the relationship between POD and POCD after cardiac surgery and determine the effects of postoperative delirium related to postoperative cognitive dysfunction and sleep disturbances on long-term prognosis.

PATIENTS AND METHODS

Between May 2010 and July 2011, 285 consecutive patients who had cardiac surgery with cardiopulmonary bypass (CPB) were prospectively enrolled in this study after the approval of the hospital's ethics committee. Patients who had cerebrovascular diseases, including dementia and postoperative stroke, were excluded from the study.

All of the patients were evaluated daily using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), which has been sufficiently validated to identify delirium in critically ill and cardiac surgical patients.[8,9] Postoperative delirium is defined according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria developed by the American Psychiatric Association (APA).[10] Based on a structured interview, the CAM-ICU algorithm consists of four clinical criteria: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. For delirium to be diagnosed, both the first and second criteria have to be present, plus either the third or the fourth criterion. In our study, the patients were assessed according to the DSM-IV criteria, and those with postoperative delirium were defined as group 1 (n=26). The patients whose preoperative and operative characteristics were similar to group A but who had no delirium were defined as group 2 (n=25). The mean age was 64±10.4 years (range, 40 to 84 years) for group 1 and 64±9.4 years (range, 42 to 77 years) for group 2 (p=0.900). For both groups, cognitive functions were evaluated at the time of hospital discharge and at the postoperative sixth and 12th months.

Cognitive function was assessed with the use of the mini-mental state examination (MMSE),[11,12] a short test focusing on global mental status that measures cognitive performance. It is specifically designed to screen for dementia and is comprised of 11 questions which concentrate on the cognitive aspects of mental function. This specificity provided a very clear impression of overall cognitive deficits. The MMSE has a score ranging from 0 to 30 points, with lower scores indicating poorer performance. A score of less than 24 indicates significant cognitive impairment and demonstrates an overall deterioration of cognitive function. The MMSE was conducted before hospital discharge and at six and 12 months after surgery.

Functional ability was assessed via the Instrumental Activities of Daily Living (IADL).[13] This questionnaire was completed by both the patient and an informant (a member of the patient's family) and contained seven questions related to the use of a telephone, commuting, shopping, preparation of meals, housework, current medications, and finances. If the patient could do the activity without assistance, the score was 0, but if some assistance was needed, the score was 1. Scores of 2 or higher on the IADL indicated the patient required assistance with daily living.

Sleep disturbances were assessed by the Pittsburgh Sleep Quality Index (PSQI),[14] which measures the quality and patterns of sleep in adults. The PSQI differentiates poor sleep from good sleep by measuring seven domains: subjective sleep quality, sleep latency,

sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. A total score of >5 indicates a poor sleeper.

We compared the rates of cognitive dysfunction of the patients in groups 1 and 2 at the postoperative 6th and 12th months. In addition, we also assessed their professional working life and functional ability along with any sleep disturbances they were having at the postoperative 12th month.

Operative techniques

All surgery was performed using general anesthesia. The standardized anesthetic management was composed of midazolam (0.1-0.15 mg/kg) and fentanyl (15-25 μg/kg) in all of the patients. A neuromuscular blockade was achieved by the infusion of 0.1 mg/kg/h vecuronium bromide, and the lungs were ventilated to normocapnia using a 50% nitrous oxide oxygen mixture. A fentanyl infusion (2-5 μg/kg/hour), a midazolam infusion (50-80 μg/kg/hour), and isoflurane were used to maintain anesthesia. Standard surgical techniques were used, and these did not change. All of the patients underwent standard nonpulsatile hypothermic (30 °C to 34 °C) cardiopulmonary bypass (CPB) using a membrane oxygenator (Dideco Compactflo Evo, Sorin Group Italia S.R.L., Mirandola, Italy), roller pump, and an arterial line filter. Nonpulsatile perfusion of 2 to 2.6 L/min/m^2 was maintained throughout CPB. The pump was primed with a crystalloid solution to achieve a hematocrit of ≥24% during extracorporeal circulation and packed red blood cells (RBCs) were added when necessary to achieve the desired hematocrit. All of the patients underwent CPB through an ascending aortic cannula. Throughout the surgery, arterial carbon dioxide tension was maintained at 35 to 40 mmHg with a partial pressure of oxygen at 150 to 250 mmHg.

Statistical analysis

Statistical analysis was performed by SPSS (SPSS Inc., Chicago, Illinois, USA) for Windows version 16.0. Continuous data was given as mean ± standard deviation (SD) while categorical data was expressed using percentages (%). For comparison of the continuous variables, Student's t-test and a descriptive test were used while a chi-square test was used to analyze the relationships between categorical data. A *p* value of less than 0.05 was considered to be significant.

RESULTS

Postoperative delirium occurred in 26 (9.1%) of the 285 prospective patients. Of the 51 patients enrolled in the study, eight died during the one-year follow-up period, and 43 completed the MMSE three times. The characteristics of all of the patients are summarized in Table 1. The demographic and medical data were similar in the two groups, and there was no statistically significant difference in mortality at the postoperative 12th month (p=0.240). Additionally, there were no significant differences in terms of age and gender between the two groups. However, there were no significant differences regarding the type of surgical procedure and characteristics of the patients in the two groups., We also discovered that the duration of

Table 1. Characteristics of the delirium and non-delirium patients after cardiac surgery

	Delirium patients (n=26)			Non-delirium patients (n=25)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			64.4±10.4			64.8±9.4	0.900
Female	6	23.1		4	16.0		
Male	20	76.9		21	64.0		0.720
APACHE II scores			5.88±1.94			5.16±1.14	0.140
Body mass index (kg/m^2)			28.73±2.53			28.60±4.53	0.890
Chronic obstructive pulmonary disease	3	11.5		1	4		0.610
Hypertension	20	76.9		14	56.0		0.140
Diabetes mellitus	9	34.6		10	40.0		0.770
Smoking	11	42.3		7	28		0.380
Alcohol use	4	15.4		0	0		0.110
Emergency operation	3	11.5		0	0		0.230
Coronary artery bypass graft	20	76.9		25	100		0.230
Time in intensive care unit			3.69±1.85			1.60±0.57	<0.001
Time in hospital (days)			10.12±3.84			7.32±1.37	<0.001
Mortality (12 months)	6	23.1		2	8.0		0.240

SD: Standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation.

Table 2. Comparison of the mini-mental state examination scores of the delirium and non-delirium patients

	Total patients	Delirium patients		Non-delirium patients		
	n	n	Mean±SD	n	Mean±SD	*p*
MMSE scores (Before hospital discharge)	51	26	26.00±1.41	25	28.64±1.07	<0.001
MMSE scores (Postoperative 6th month)	49	24	26.71±1.51	25	29.28±1.02	<0.001
MMSE scores (Postoperative 12th month)	43	20	28.00±1.68	23	29.91±0.28	<0.001

SD: Standard deviation.

ICU stay was significantly longer in group 1 with an average of 3.6 days versus 1.6 days in group 2 (p<0.001). The same was true for length of hospital stay with an average of 10.1 days in group 1 and 7.3 days in group 2 (p=0.001).

A comparison of the MMSE scores in groups 1 and 2 are given in Table 2. The mean MMSE scores were statistically significantly lower in group 1 (26.0) than in group 2 (28.6) (p<0.001). The scores were also lower in group 1 at the postoperative sixth month (26.7) than in group 2 (29.2). The trend continued in the postoperative 12th month with an average score of 28.0 in group 1 versus 29 in group 2 (p<0.001). There were four patients in group 1 with MMSE scores ≤24 at hospital discharge, but none at the postoperative 12th month. In addition, the mean MMSE scores statistically significantly improved for group 1 from 26.0 at discharge to 28.6 at the postoperative 12th month. The statistically significant improvement also occurred in group 2 with the scores increasing from 28.0 to 29.9 over the same time period (p<0.001).

The results of a comparison between the groups regarding sleep disturbances, professional working life, and assistance required during daily activities at the postoperative 12th month are given in Table 3. The number of patients who suffered from sleep disturbances was significantly higher in group 1 (73.1%) than in group 2 (32.0%) 12 months after surgery (p<0.001). However, there were no statistically significant differences with regard to professional working life (p=1.000) or the number of patients requiring assistance during daily activities (p=0.290).

DISCUSSION

Cognitive impairment after cardiac surgery is becoming more relevant, especially in the elderly. The two main entities of postoperative cognitive decline, POD and POCD, are frequently thought to have the same clinical scenarios. Although they both represent cognitive dysfunction after surgery, they differ in numerous ways, with delirium being well-defined and acute at onset and POCD being chronic with a longer duration.

The etiology of POCD is unknown. Increased age, prior cognitive decline, DM, and hypertension are well-known risk factors. Previous studies have shown that POCD occurs more frequently with cardiac surgery than with other forms of surgery, with CPB being the primary contributor. However, a recent study by Farhoudi et al.[15] revealed that off-pump cardiac surgery also had a similar incidence of POCD compared with POD.

Some previous studies have suggested that postoperative delirium and cognitive dysfunction may occur more frequently in patients undergoing valve surgery, either with or without CABG, compared with those having CABG surgery alone one week after surgery.[16] We did not observe a relationship between the type of operation and delirium or cognitive decline, but this could have been related to the relatively small size of our study population.

Table 3. Comparison of the delirium and non-delirium patients at the postoperative 12th month

	Delirium patients		Non-delirium patients				
	n	%	n	%	*p*	OR	CI
Professional working life	9	34.6	8	32.0	1.000	1.12	0.35-3.60
Sleep disturbances*	19	73.1	5	20.0	<0.001	10.85	2.93-4.16
Assistance required in daily activities**	7	26.9	3	12.0	0.290	2.70	0.612-11.93

OR: Odds ratio; CI: Confidence interval; * The Pittsburgh Sleep Quality Index (PSQI) scores >5, ** Instrumental Activities of Daily Living scores >2.

We found that postoperative delirium was linked to postoperative cognitive dysfunction after cardiac surgery. Several studies have suggested that in addition to the immediate effects of postoperative cognitive dysfunction, long-term outcome measures are also affected.[1,17,18] Furthermore, the presence of delirium during ICU hospitalization also increases the risk of an anxiety disorder for up to two years after discharge.[19] Multiple studies have also confirmed the association between delirium during hospitalization and impairment in memory, attention, and concentration for up to nine to 12 months following discharge.[19-21] These impairments complicate early recovery and strongly affect the postoperative quality of life (QOL). In our study, we found that significantly lower MMSE scores were an indicator of cognitive decline in patients with postoperative delirium (group 1) during the first postoperative year after cardiac surgery.

The study by Newman et al. focused on the impact of POCD on QOL one year after cardiac surgery,[3] and they found that cognitive decline is significantly associated with a decreased ability to engage in activities of daily living, less functional capacity, more depression, more self-reported mental difficulties, greater symptom limitations, and a less positive general health impression. They also demonstrated that cognitive decline which occurs after surgery limits the anticipated improvement in QOL accomplished by surgical coronary revascularization. Contrary to their results, we did not find any significant differences in terms of professional working life and daily activities at the postoperative 12th month. On the other hand, we found that the prevalence of sleep disturbances, especially excessive daytime sleep or unqualified sleep, were significantly more common in patients with delirium (group 1) 12 months after surgery.

Sleep disturbances are common in patients suffering from cognitive decline.[22,23] As a result of any of the previously mentioned psychological conditions or independent events, ICU stay may lead to sleep disturbances.[21] A study by Jaussent et al.[24] stated that excessive daytime sleep may be associated independently with the risk of cognitive impairment in the elderly. It may also be an early marker and a potentially reversed risk factor of cognitive decline. In another study, over 60% of patients with mild cognitive impairment reported one or more sleep disturbances;[25] therefore, a careful clinical evaluation should be routinely performed in a clinical setting for persons with cognitive decline who suffer from this symptom.

In conclusion, our findings suggest that postoperative development of delirium substantially correlates with postoperative cognitive dysfunction and should be added to the list of risk factors for prolonged impairment after cardiac surgery. Postoperative cognitive decline which occurs after cardiac surgery is a noteworthy complication that has important implications on postoperative prognosis. These cognitive difficulties can have a major impact on QOL after hospitalization. By preoperatively identifying the patients at high risk for postoperative delirium, postoperative preventive strategies can be implemented which might reduce long-term cognitive decline.

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