Int J Burn Trauma 2022;12(4):161-167
www.IJBT.org /ISSN:2160-2026/IJBT0140203

Original Article

The effect of melatonin on prevention of postoperative delirium after lower limb fracture surgery in elderly patients: a randomized double blind clinical trial

Mohammad Reza Fazel[1], Saba Mofidian[1], Mehrdad Mahdian[2], Hossein Akbari[3], Mohammad Reza Razavizadeh[1]

[1]Kashan University of Medical Sciences, Department of Anesthesiology, Kashan, Iran; [2]Trauma Research Center, Kashan University of Medical Sciences, Kashan, Iran; [3]Social Determinants of Health (SDH) Research Center, Kashan University of Medical Sciences, Kashan, Iran

Received October 30, 2021; Accepted July 5, 2022; Epub August 15, 2022; Published August 30, 2022

Abstract: Background: Postoperative delirium is a common complication with a high morbidity rate. This study was designed to consider the effectiveness of melatonin in prevention and treatment of postoperative delirium. Methods: Seventy-two patients aged >60 years old with Abbreviated Mental Test (AMT) >8 scheduled for orthopedic surgery under spinal anesthesia, were randomly distributed equally to melatonin or placebo groups. In the melatonin group, the patients were given 5 mg melatonin capsules orally the night before surgery, the night of the operation, and two nights after the surgical operation at 9 pm. Likewise, in the placebo group, the patients received placebo in the same times. For diagnosis of postoperative delirium, the AMT test was used before the operation and three days after that. The Generalized estimating equations model (GEE) with logit link to Multivariate analysis was used in the study and P<0.05 was considered statistically significant. Results: In total, 72 patients completed the study. Thirty-three patients (45.8%) were male with a mean (SD) age 71.4 (3.6) years. On the first day after the surgery, the incidence of delirium was significantly lower in the melatonin group compared to the placebo group (22.2% vs. 44.4%, P=0.046). On the second and third days after the surgery, the level of delirium in the melatonin group was also significantly lower than that in the placebo one. The GEE model showed a significant interaction between time and treatment groups. Conclusion: The findings of the study showed that melatonin prevented delirium after the orthopedic surgeries in the elderly patients and could be useful for the patients as such.

Keywords: Melatonin, delirium, surgery, orthopedics, aged

Introduction

Delirium, a serious disturbance in mental abilities with the main features of inattention and global cognitive dysfunction that makes it costly and potentially fatal, affects nearly 50 percent of the elderly hospitalized per year [1]. Also, 10 to 30 percent of those hospitalized for any reason have a chance of developing the delirium. Prevalence of delirium in the ICU patients and cardiac patients admitted to CCUs were 30 and 40%, respectively [2]. Causes of delirium include drug poisoning, tumors, trauma, infection, cardiovascular disorders, metabolic disorders; and endocrine and nutritional disorders. Risk factors for delirium include age, gender, depression; dementia and anxiety. Blood transfusion has also been reported in various studies as a delirium risk factor [3, 4]. Although delirium is not one of the most common complications of the orthopedic surgery, it has received special attention in the recent years [5-7]. Many studies have shown this complication after orthopedic surgery, especially in the elderly patients. In other words, risk of delirium in patients older than 70 years of age increased more than 3.78 folds than other patients (OR 3.78; 95% CI 2.97-4.80) [8]. Patient's health impairment and increasing health care costs due to delayed functional recovery and prolonged hospital stay may be examples of postoperative delirium consequences [9]. With regard to the consequences, prevention of delirium is of a major importance. Circadian rhythm may be affected by sleep disorders in elderly patients, especially after surgi-

cal operations. This can be due to degeneration of the suprachiasmatic nuclei, which results in a decreased blood melatonin level [10]. Moreover, it has been found that melatonin levels decrease after the surgery [11]. Sleep disturbances result in serious physiological consequences such as delirium which may negatively influence the patients' outcomes [12]. From the aforementioned, what can be concluded from these hypotheses is that delirium can be prevented by improving the patient's sleep quality. On the one hand it is clear that the timed melatonin administration, can be used to manage sleep disorders [13] and on the other hand, some studies have shown that melatonin may reduce delirium [14, 15]. However, the experimental data are rather controversial, and there is no general agreement about melatonin administration and reducing delirium. As some studies have also suggested that melatonin levels were not significantly different in the patients with and without delirium [16, 17]. Given the inconsistencies in these studies as well as the limited studies in this area and to test the hypothesis that short-term administration of oral melatonin will reduce the incidence of postoperative delirium in the elderly patients undergoing elective orthopedic surgeries, this randomized controlled trial was designed. Because delirium is more common in the elderly, this study was performed in the elderly patients. On the other hand, due to the nature of this study (clinical trial) and random selection of the samples in both groups, the effect of age was removed as a confounding variable.

Materials and methods

The study protocol was approved both by the Ethics Committee of the Deputy of Research and Technology, Kashan University of Medical Sciences (Ethics committee approval number: IR.KAUMS.MEDNT.REC.1398.007) and by the Iranian Clinical Trial Registry (ID number: IRCT20190419043320N1). This double-blind, randomized, placebo-controlled clinical trial study was carried out between May and November 2019 in Kashan Shahid Beheshti hospital (affiliated to Kashan University of Medical Sciences), Kashan, Iran, to assess the efficacy of oral melatonin in reducing delirium in the elderly patients undergoing orthopedic surgery under spinal anesthesia. The sample size estimation was based on a primary outcome of a reduction in delirium symptoms in Fan Y et al. (2017) study [16]. Written informed consent was taken from all the patients by an anesthesiologist who was involved in the study.

Seventy-two patients over 60 years of age undergoing femoral fracture surgery and knee or hip arthroplasty were randomly recruited two equal groups through permuted block randomization: group M (melatonin) and group P (placebo). Eligibility criteria for the study participation were age more than 60 years along with an Abbreviated Mental Test (AMT) result more than 8. The following exclusion criteria were applied: a history of alcohol or psychotropic drugs consumption, sensory disorders, including blindness and hearing loss, cognitive disorders and dementia; severe underlying diseases including severe infection, severe anemia, seizures, stroke and cerebral hemorrhage; heart disease including acute myocardial infarction, congestive heart failure and arrhythmia, and medications including anticonvulsants, antihistamines, and psychotropic drugs. After recruiting the patients, Abbreviated Mental Test (AMT) was used to detect the delirium. This test was performed just the day before the surgery for all the patients and their score was recorded. The test consists of ten questions and each question correctly answered scores one point. If the patients' score was more than 8, they were randomly assigned to one of the study groups (M) or (P). A score of less than 8 suggests cognitive impairment at the time of testing [18]. The randomization list was computer-generated using online software (https://www.sealedenvelope.com/simple-randomiser/v1/lists) in blocks of 4 patients to avoid disproportionate numbers of the patients in each group.

All the study participants included patients as well as scientific and medical personnel which were all blind to the group assignment. An independent person had the task of randomizing and maintaining codes and labeling the products.

In the (M) group, the patients were given 5 mg melatonin capsules (Now Food, Bloomingdale, IL 60108, USA) orally just the night before the surgery, the night of the operation and two nights after the surgical operation at 9 pm. In the (P) group, the patients received placebo (as Avisel capsules) in the mentioned times. All the patients received spinal anesthesia. Before the

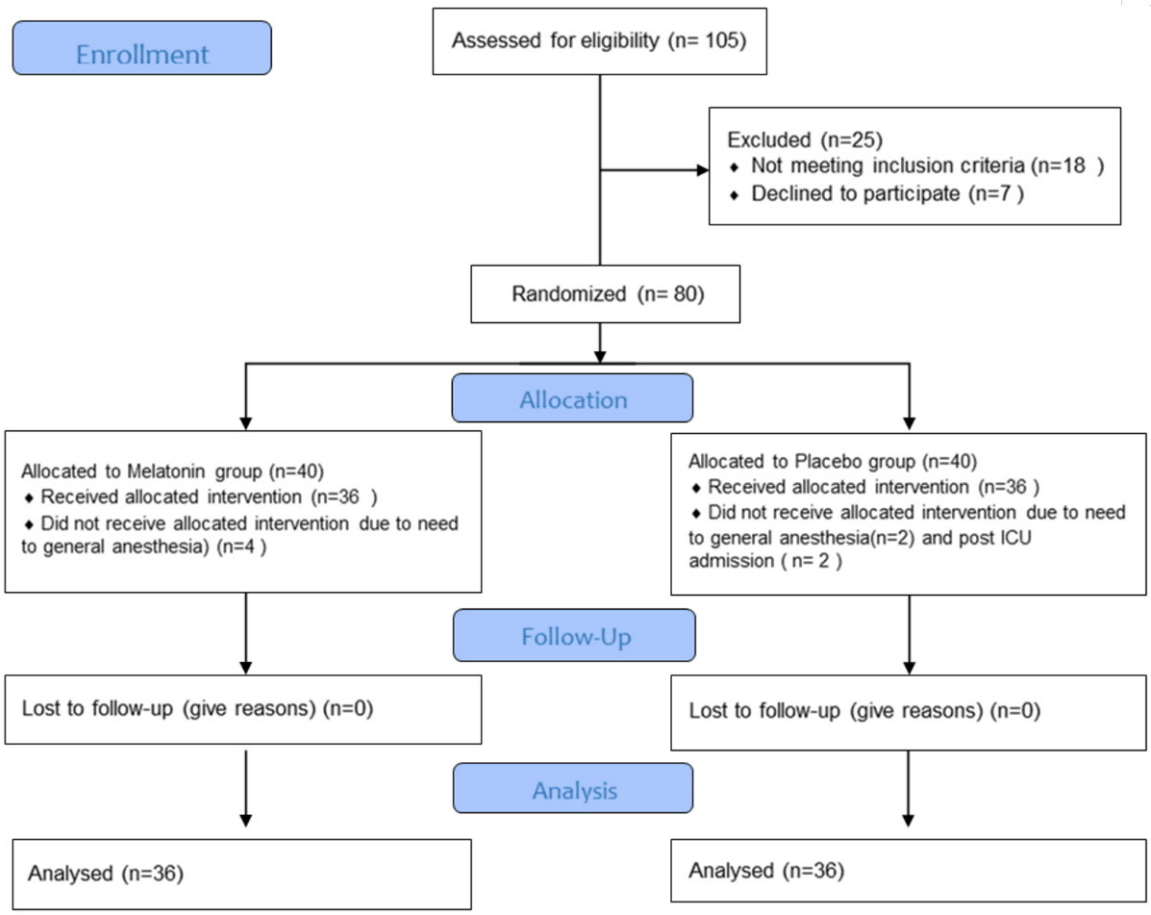

Figure 1. Consort Flow Diagram of the study.

anesthesia, the patients received 500 ml lactated ringer's solution. Spinal anesthesia was carried out using a 25-gauge needle after skin prep using 10% povidone iodine prep solution. Hyperbaric bupivacaine 0.5% (15 mg) was used as an anesthetic solution which was administered between L4-L5 or L5-S1. All the patients received oxygen at 5 L/min during the procedure. The patients were excluded from the study if spinal anesthesia was not successful or the patients underwent general anesthesia for any reason. In both groups, bleeding was assessed during and after surgery and appropriate fluids or transfusion was performed if needed. Sedation was performed during the surgery using midazolam 0.3 mg kg-1 intravenously. All patients were monitored for at least 2 hours in post anesthesia care unit and then transferred to the ward if the conditions were stable. For diagnosis of probable postoperative delirium, the AMT test was used at day of operation, and three days after surgical operation (four days in total). The randomization codes were opened only after the final data analysis.

Statistical analysis

The data were compared in the two groups using Chi-square test. Multivariate analysis was also performed using generalized estimating equations model (GEE) with logit link. To select the best model, deviance was used as a goodness-of-fit criterion. For statistical analyses, SPSS statistical software (version 16.0, SPSS Inc. Chicago, IL) was used. A $P<0.05$ was considered statistically significant.

Results

During the study period, a total of 105 patients were screened. Thirty-three were excluded and finally 72 patients were enrolled and randomized to either melatonin (no=36) or placebo (no=36) groups (**Figure 1**). The demographic and clinical characteristics of the patients in

Table 1. Demographics and clinical characteristics in the two groups of the study

variables	Status	Study Group		*P* Value*
		Melatonin	Placebo	
Gender	Male	16 (44.4)	17 (47.2)	0.813
	female	20 (55.6)	19 (52.8)	
Age	<75	29 (80.6)	28 (77.8)	0.772
	≥75	7 (19.4)	8 (22.2	
Type of Operation	Pelvis	12 (33.3)	12 (33.3)	0.959
	Femur	11 (30.6)	10 (27.8)	
	Knee	13 (36.1)	14 (38.9)	
Delirium Day 1	Yes	8 (22.2)	16 (44.4)	0.046
	No	28 (77.8)	20 (55.6)	
Delirium Day 2	Yes	6 (16.7)	14 (38.9)	0.035
	No	30 (83.3)	22 (61.1)	
Delirium Day 3	Yes	2 (5.6)	11 (30.6)	0.006
	No	34 (94.4)	25 (69.4)	

*Chi-Square test.

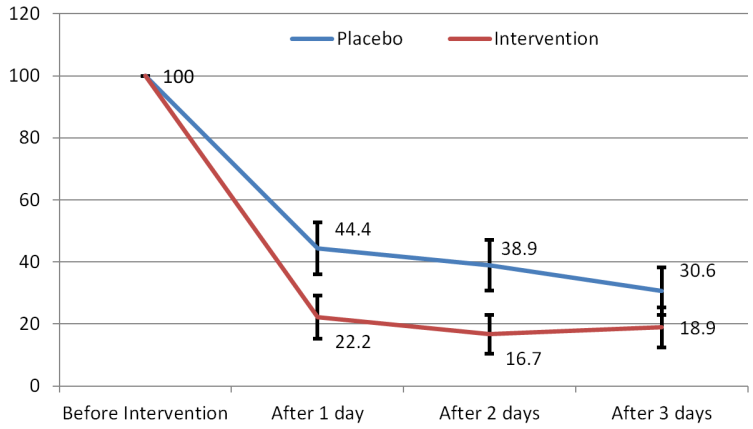

Figure 2. Frequency of delirium in the two groups of the study in the days after the surgery.

the control groups are summarized in **Table 1**. There were no statistically significant differences between the two groups of the study regarding demographic characteristics and the type of surgery. The incidence of delirium in the melatonin-treated group was significantly lower than that in the placebo group in all three days after the surgical operation (**Table 1** and **Figure 2**). However, considering the delirium incidence such as type of the surgery and sex separately in the subgroups of the study, there was no significant difference in most subgroups (**Table 2**).

The results of the generalized estimating equations model (GEE) showed that the effect of time on delirium changes was significant. In other words, the delirium changes are not the same over the time (P=0.012) (**Table 3**). The time - group interaction was also significant as the delirium changes. This indicates that the delirium changes in the two treatment groups are not the same over the time (P=0.031) (**Table 3**).

Discussion

The present study showed that the incidence of delirium was significantly lower in the melatonin-treated group every three days after the surgical operation than that in the placebo group. Postoperative delirium is a major challenge for health care providers. Elderly patients particularly are more susceptible to postoperative delirium. Although delirium is a multifactorial disorder after surgery, its only definitive risk factor is aging [19]. These findings suggest that elderly patients undergoing major surgeries have a high rate of delirium after surgery [20]. The etiology of postoperative delirium has not been fully understood, and the results of previous studies have been controversial [1]. Although the mechanisms behind postoperative delirium remain unclear, potential risk factors for postoperative delirium have been suggested. Among the many explanations for the development of postoperative delirium, postoperative sleep disorders are more prominent [20, 21]. Circadian sleep disorders are also common in the elderly patients after surgery that appear to increase cardiovascular instability, adversely affect the immune system, increase metabolism, and prolong recovery time. These disorders are often associated with neuropsychiatric symptoms and allow the development of a common underlying pathological correlate [22]. Therefore, the use of melatonin seems to be reasonable among the various pharmacological agents [23-26]. The results of

Table 2. Frequency distribution of delirium on different days after surgery in the two groups according to the type of surgery and patients' gender

Variables		Groups	Day 1 after surgery		Day 2 after surgery		Day 3 after surgery	
			No (%)	*P value*	No (%)	*P value*	No (%)	*P value*
Type of Operation	Pelvis	Melatonin	4 (33.3)	0.041	4 (33.3)	0.102	2 (16.7)	0.083
		Placebo	9 (75)		8 (66.7)		6 (50)	
	Femur	Melatonin	2 (18.2)	0.525	2 (18.2)	0.525	0 (0)	0.119
		Placebo	3 (30)		3 (30)		2 (20)	
	Knee	Melatonin	2 (15.4)	0.410	0 (0)	0.077	0 (0)	0.077
		Placebo	4 (28.6)		3 (21.4)		3 (21.4)	
Gender	Male	Melatonin	1 (6.3)	0.019	1 (6.3)	0.041	0 (0)	0.019
		Placebo	7 (41.2)		6 (35.3)		5 (29.4)	
	Female	Melatonin	7 (35)	0.433	5 (25)	0.257	2 (10)	0.095
		Placebo	9 (47.4)		8 (42.1)		6 (31.6)	

Chi-Square test.

Table 3. Generalized estimating equations model coefficients based on logit link regarding effect of therapeutic group variables and time of the study and their interactions

Parameter	B	Std. Error	95% Wald CI		Hypothesis Test*		
			Lower	Upper	Wald Statistics	df	Sig.
(Intercept)	.223	.3354	-.434	.881	.443	1	<0.001
[day =3.00]	.229	.1576	-.080	.538	2.108	1	0.012
[day =2.00]	2.610	.8648	.915	4.305	9.110	1	
[group =1.00] * [day =3.00]	1.157	.5629	.054	2.261	4.228	1	0.031
[group =1.00] * [day =2.00]	-2.012	.8126	-3.605	-.420	6.132	1	
[group =1.00] * [day =1.00]	1.030	.5227	.005	2.054	3.880	1	

*The control group and the first day of the study were considered as baseline.

this study are in accordance with the findings of previous works in this field. Fan Y et al. (2017) showed that cognitive impairments of delirium decreased after treatment with melatonin. They therefore suggested that melatonin supplements, which improve sleep quality, could prevent or treat delirium after hip arthroplasty [16]. Sultan et al. (2010) found in the patients undergoing arthroplasty that Melatonin was successful in decreasing postoperative delirium when used preoperatively. They also showed that melatonin administration at three nights after the surgery could cure more than half of all the delirium patients [14]. In another study, Al-Aama and his colleagues (2010) during a randomized clinical trial concluded that Melatonin was associated with a lower risk of delirium versus placebo in the elderly patients admitted through the emergency department to Internal Medicine in-patient services [15]. However, the findings of the current study do not support some previous research in this field. In contrast to our findings, Hansen et al. (2014) showed that melatonin increased efficacy and sleep duration but did not affect cognitive function and delirium following breast surgery in the cancerous patients. A possible explanation for the difference in our results with Hansen's finding may be due to differences in the study population, neuropsychological tests, and the timing of cognitive tests. On the other hand, Rikie M. Scholtens et al. (2016) showed that there was no significant difference between elderly patients with or without delirium who were acutely admitted for surgical repair of a hip fracture regarding CSF melatonin concentration levels [17]. Nevertheless, Y Wu et al. (2014) have shown that dysregulated melatonin levels correlate with postoperative delirium and support the hypothesis that sleep disorders are associated with postoperative delirium [27]. Synthetic melatonin supplements have been used to improve sleep quality [22]. It has also been shown that melatonin can

improve sleep efficiency and total sleep time using polysomnography [28]. All of that being said, we should be cautious about the role of melatonin in the prevention and treatment of post-operative delirium because delirium is a multifactorial disorder and all of the mechanisms behind it are not well understood. Therefore, further studies on the role of melatonin in the recovery of cognitive disorders are suggested.

Finally, a number of important limitations need to be considered. First, the numbers of patients and controls in our study were relatively small. Hence, the interpretation of the results should be cautious. Second, this study was performed on the elderly patients and the results can not be generalized to all age groups. Third, the present study has no long-term follow-up and so, some patients may develop delirium after our study period. Further study with larger sample size and longer period is recommended.

Conclusion

The findings of the present study showed that the dose of 5 mg melatonin orally the night prior to and three days following the surgical operation prevents delirium after orthopedic surgeries in the elderly patients. Subgroup analysis also showed that there were no significant differences between the delirium incidence in the subgroups of the study regarding gender and type of the surgery.

Acknowledgements

The initial ideation of this article has been sprung from a thesis proposition by Dr. Saba Mofidian, a resident of anesthesiology at Kashan University of Medical Sciences. The authors are grateful to the Deputy Research of Kashan University of Medical Sciences for generous support of this work (Grant No. 97221).

Disclosure of conflict of interest

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Address correspondence to: Mehrdad Mahdian, Trauma Research Center, Kashan University of Medical Sciences, Kashan, Iran. Tel: +98 9133626687; ORCID: 0000-0002-9168-6372; E-mail: mmahdian78@gmail.com

References

[1] Inouye SK, Westendorp RG and Saczynski JS. Delirium in elderly people. Lancet 2014; 383: 911-922.

[2] Kim Y and Hong SJ. Intensive care unit delirium. Korean J Crit Care Med 2015; 30: 63-72.

[3] Oh ES, Fong TG, Hshieh TT and Inouye SK. Delirium in older persons: advances in diagnosis and treatment. JAMA 2017; 318: 1161-1174.

[4] Bilotta F, Lauretta M, Borozdina A, Mizikov V and Rosa G. Postoperative delirium: risk factors, diagnosis and perioperative care. Minerva Anestesiol 2013; 79: 1066-1076.

[5] Urban MK, Sasaki M, Schmucker AM and Magid SK. Postoperative delirium after major orthopedic surgery. World J Orthop 2020; 11: 90.

[6] Velagapudi R, Subramaniyan S, Xiong C, Porkka F, Rodriguiz RM, Wetsel WC and Terrando N. Orthopedic surgery triggers attention deficits in a delirium-like mouse model. Front Immunol 2019; 10: 2675.

[7] Song KJ, Ko JH, Kwon TY and Choi BW. Etiology and related factors of postoperative delirium in orthopedic surgery. Clin Orthop Surg 2019; 11: 297-301.

[8] Yang Y, Zhao X, Gao L, Wang Y and Wang J. Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. Aging Clin Exp Res 2021; 33: 1493-1506.

[9] Parikh SS and Chung F. Postoperative delirium in the elderly. Anesth Analg 1995; 80: 1223-1232.

[10] Hanania M and Kitain E. Melatonin for treatment and prevention of postoperative delirium. Anesth Analg 2002; 94: 338-339.

[11] Cronin AJ, Keifer JC, Davies MF, King TS and Bixler EO. Melatonin secretion after surgery. Lancet 2000; 356: 1244-1245.

[12] Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G and Puntillo KA. Sleep and delirium in ICU patients: a review of mechanisms and manifestations. Intensive Care Med 2009; 35: 781-795.

[13] Burman D. Sleep disorders: circadian rhythm sleep-wake disorders. FP Essent 2017; 460: 33-36.
[14] Sultan SS. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. Saudi J Anaesth 2010; 4: 169.
[15] Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J and Dasgupta M. Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. Int J Geriatr Psychiatry 2011; 26: 687-694.
[16] Scholtens RM, van Munster BC, van Faassen M, van Kempen MF, Kema IP and de Rooij SE. Plasma melatonin levels in hip fracture patients with and without delirium: a confirmation study. Mech Ageing Dev 2017; 167: 1-4.
[17] Scholtens RM, de Rooij SE, Vellekoop AE, Vrouenraets BC and van Munster BC. Preoperative CSF melatonin concentrations and the occurrence of delirium in older hip fracture patients: a preliminary study. PLoS One 2016; 11: e0167621.
[18] Lam SC, Wong YY and Woo J. Reliability and validity of the abbreviated mental test (Hong Kong version) in residential care homes. J Am Geriatr Soc 2010; 58: 2255-2257.
[19] Evered L, Silbert B, Scott DA, Ames D, Maruff P and Blennow K. Cerebrospinal fluid biomarker for Alzheimer disease predicts postoperative cognitive dysfunction. Anesthesiology 2016; 124: 353-361.
[20] Krenk L, Rasmussen LS and Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. Acta Anaesthesiol Scand 2010; 54: 951-956.
[21] Gögenur I, Middleton B, Burgdorf S, Rasmussen LS, Skene DJ and Rosenberg J. Impact of sleep and circadian disturbances in urinary 6-sulphatoxymelatonin levels, on cognitive function after major surgery. J Pineal Res 2007; 43: 179-184.
[22] Walker MP. Cognitive consequences of sleep and sleep loss. Sleep Med 2008; 9: S29-S34.
[23] Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, Chen KS, Gu XE and Zhu SN. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. Crit Care Med 2012; 40: 731-739.
[24] Prakanrattana U and Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care Med 2007; 35: 714-719.
[25] Gamberini M, Bolliger D, Lurati Buse GA, Burkhart CS, Grapow M, Gagneux A, Filipovic M, Seeberger MD, Pargger H, Siegemund M, Carrel T, Seiler WO, Berres M, Strebel SP, Monsch AU and Steiner LA. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. Crit Care Med 2009; 37: 1762-1768.
[26] Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Byrne AJ, Hudetz AG, Warltier DC and Pagel PS. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2009; 23: 651-657.
[27] Wu Y, Wang J, Wu A and Yue Y. Do fluctuations in endogenous melatonin levels predict the occurrence of postoperative cognitive dysfunction (POCD)? Int J Neurosci 2014; 124: 787-791.
[28] Huang HW, Zheng BL, Jiang L, Lin ZT, Zhang GB, Shen L and Xi XM. Effect of oral melatonin and wearing earplugs and eye masks on nocturnal sleep in healthy subjects in a simulated intensive care unit environment: which might be a more promising strategy for ICU sleep deprivation? Crit Care 2015; 19: 124.