

Effects of Melatonin on Postoperative Delirium After PCI in Elderly Patients: A Randomized, Single-Center, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Experimental evidence has indicated the benefits of melatonin (Mel) for the treatment of delirium. Clinical trials had no definite conclusions concerning Mel on delirium after percutaneous transluminal coronary intervention (PCI) in elderly patients. The present study explored whether acute Mel treatment could reduce the incidence of delirium.

Methods: This trial enrolled patients over the age of 60, who were admitted to intensive care units (ICUs) after PCI. A computer-generated randomization sequence (in a 1:1 ratio) was used to randomly assign patients to receive Mel (3 mg/day) or placebo once daily for up to 7 days. The primary endpoint was the incidence of delirium, assessed twice daily with the Confusion Assessment Method (CAM) during the first 7 postoperative days. Analyses were performed using intention-to-treat and safety populations.

Results: A total of 297 patients randomly were assigned to receive either placebo ($N = 149$) or Mel ($N = 148$). The incidence of postoperative delirium was significantly lower in the Mel group than in the placebo group (27.0% vs. 39.6%, respectively, $P = 0.02$). There was no significant difference between 30-day all-cause mortality (12.2% vs. 14.1%, $P = 0.62$) and drug reactions (0 vs. 2.0%, $P = 0.25$). The length of stay and hospitalization costs in the Mel group were significantly decreased compared with those in the placebo group ($P > 0.05$).

Conclusion: The current study suggests that Mel is safe and effective in the treatment of delirium after PCI. Further investigation is necessary to fully understand the potential usefulness of Mel in older patients via larger randomized, multicenter, double-blind, and placebo-controlled trials.

INTRODUCTION

Delirium is a common, life-threatening, typical clinical syndrome with the main clinical manifestations of temporary organic mental disorder, acute brain dysfunction, and changes in cognitive function and disorientation, which can

lead to long-term cognitive impairment and increased disability, mortality, length of hospital stay and hospitalization costs [Gleason 2015]. The prevalence of delirium is reported to be up to 74% in critically ill patients [Milbrandt 2004]. In a previous report, approximately 60–80% of hospitalized older adults had delirium [Girard 2010]. More than 20% of patients who stay in the intensive care unit (ICU) are diagnosed with delirium [Mather 2017]. In recent years, with growth in the aging population, the number of older patients undergoing surgery has increased, and the incidence of postoperative delirium after surgery in older patients has been reported to be as high as 46% [Saczynski 2012]. In the United States, more than 2.6 million adults older than 65 years of age develop delirium each year, accounting for an estimated annual health care expenditure of more than \$164 billion. Additionally, delirium or postoperative delirium may increase the long-term risk of dementia and mortality [Redelmeier 2019]. In the past 20 years, the treatment of delirium in older patients has become a severe challenge. Al Tmimi et al. [Al Tmimi 2020] reported that postoperative delirium was reported in 41% of patients undergoing cardiac surgery. As the elderly population grows, an increasing number of patients suffer from acute myocardial infarction, coronary artery sclerosis, and unstable angina, and more patients receive percutaneous transluminal coronary intervention (PCI). The incidence of postoperative delirium in elderly patients is increasing. However, the diagnosis and treatment of postoperative delirium are relatively difficult, and there is no specific drug treatment, which also makes the treatment of postoperative delirium after PCI severely challenging. To date, there have been no specific drugs for the treatment or prevention of delirium. Importantly, most drugs currently available in the clinic have no specific effect on delirium, and there also is a lack of evidence-based medicine with regard to treatment of the disease.

Melatonin (N-acetyl-5-methoxytryptamine; Mel), secreted by the pineal gland, is a potent free-radical scavenger and broad-spectrum antioxidant [Liu 2019] that easily passes through the blood brain barrier (BBB) without toxicity in large doses [Chen 2014]. Many studies have shown that Mel administration can attenuate early brain injury (EBI), cerebrovascular spasms (CVS), and brain edema following subarachnoid hemorrhage (SAH) and the consequent inflammatory response, reactive oxygen species (ROS) generation, and oxidative stress in the brain [Liu 2019; Chen 2014; Dong 2016]. Some studies also have confirmed that sleep deprivation is an important contributor to delirium in patients, and melatonin can significantly improve sleep disorders and reduce the incidence of delirium

Received June 15, 2021; received in revised form July 29, 2021; accepted July 30, 2021.

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[RE 2020]. Han et al. [Han 2020] reported a retrospective study in which melatonin and its analogs were effective in the treatment of postoperative delirium, but more evidence is needed to confirm their efficacy after cardiac surgery. In particular, the efficacy of melatonin in the treatment of delirium in patients after PCI remains unclear. The present study, therefore, explored whether Mel treatment could reduce postoperative delirium and improve clinical outcomes after PCI.

METHODS

Study design: This was a randomized, double-blind, parallel-arm, placebo-controlled trial in Jiangsu between January 1, 2018, and January 1, 2020. The study was designed to assess the superiority of the intervention. The study protocol received ethics committee approval from all participating centers. Written informed consent was obtained from patients whose competence was established by their accurate orientation for time, place, and person, as well as an understanding of the recruiter's description of the trial or otherwise from their next of kin or their legal representative. Patients randomly were assigned (1:1) to receive 3 mg/day Mel or placebo within 7 days after PCI. (Figure 1) Mel or placebo were administered orally for up to 7 days after PCI. The final follow up was 30 days after surgery.

Study patients, inclusion criteria, and exclusion criteria: Eligible patients were more than 60 years old who underwent PCI in the ICU. The inclusion criteria were as follows: (1) age more than 60 years; (2) could be randomized and received Mel or placebo within 7 days after surgery; and (3) underwent PCI under general anesthesia and were admitted to the ICU. The exclusion criteria were as follows: (1) likely unsalvageable on admission; (2) high cholesterol combined with diabetes; (3) brain injury or neurosurgery; (4) neurologic disease; (5) history of mental illness and epilepsy; and (6) other reasons (identified by researchers).

Randomization and masking: Permuted-block randomization was performed using a computer system with a generated allocation list of random numbers (in a 1:1 ratio) using SPSS 14.0 software (SPSS Institute, Hefei, Anhui Medical University). This was performed by a statistician not associated with the project team to protect the blinding and integrity of the study. The results of randomization were sealed in sequentially numbered envelopes and stored at the site

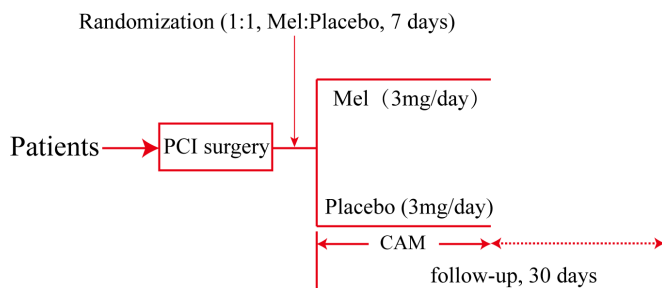


Figure 1. Study design

of the investigation until the end of the study. During the study period, all included patients were randomly assigned to receive 3 mg/day Mel or placebo within 7 days after PCI (Figure 1). A study nurse administered the study drugs based on the randomization sequence. Both the study members and patients were blinded to the study drug allocation. If an emergency occurred, such as severe hepatic failure, then two experts could request unmasking of the treatment allocation or adjust or interrupt the study drug, if necessary. All such situations were documented. Patient demographics, medical histories, and relevant investigation results were collected.

Outcome assessments and the primary endpoint: All clinical and imaging data were assessed by a masked independent diagnostic and assessment committee. This committee included two researchers, who were trained before the study and were not involved in the clinical care of patients. The primary endpoint was the incidence of delirium in the first 7 days after surgery. The first postoperative delirium evaluation was conducted approximately 24 hours after surgery and occurred twice daily (between 6 and 8 am and between 6 and 8 pm). Delirium was assessed by the Confusion Assessment Method (CAM) and the CAM for the Intensive Care Unit (CAM-ICU) [Ely 2001]. Both the CAM and CAM-ICU detected 4 features of delirium: (1) acute onset of mental status changes or a fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. To be diagnosed as delirious, a patient displayed features 1 and 2, with either 3 or 4.

Secondary endpoints: The secondary endpoints included all-cause 30-day mortality, length of stay in the ICU, and occurrence of non-delirium postoperative complications and hospital costs.

Statistical analysis: Based on previous data, it was estimated that 200 patients would be required to confirm these effects with an α of 5% and 80% power. Further assuming a 10% loss to follow up, 297 patients were enrolled [Baumgartner 2019]. A research nurse entered all baseline and outcome data in the study database. Data were collected on handwritten forms and archived in a password-protected electronic database. All continuous variables are presented as the mean \pm standard deviation. SPSS 14.0 statistical software (SPSS, Inc., Chicago, USA) was used for the statistical analyses. Independent two-sample t-tests and Spearman correlations were used to assess categorical data. Fisher's exact t-test was used to compare categorical data between two groups, and the Mann-Whitney U test was used to compare ordinal or continuous variables between groups. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Between January 1, 2018, and January 1, 2020, 355 patients were assessed. A total of 297 patients randomly were assigned to receive either placebo ($N = 149$) or Mel ($N = 148$). (Figure 2) During the study period, there was no unblinding necessary, and there was no statistically significant difference in baseline data between the two groups. (Table 1) During the study period, nine patients were lost to follow up (three in the

Table 1. Demographic and baseline characteristics of the study population in the two groups

	Placebo	Mel	P-value
Number of patients	149	148	
Age (mean±SD)	71.6±6.6	71.5±6.7	0.9
Gender	-	-	0.6
Male	89	93	
Female	60	55	
History of hypertension	-	-	0.5
Yes	112	106	
No	37	42	
Nicotine use	-	-	0.6
Yes	49	45	
No	100	103	
Type of surgery	-	-	0.4
Emergency operation	74	81	
Selective operation	75	67	
Duration of anesthesia (h, mean±SD)	2.2±0.2	2.3±0.3	0.6

Table 2. Comparison of primary endpoint-clinical outcomes between the two groups

	Placebo	Mel	P-value
Number of patients	149	148	
Delirium	39.6% (59/149)	27% (40/148)	0.02
30-day all-cause mortality	14.1% (21/149)	12.2% (18/148)	0.62

control group and six in the Mel group). All other patients were included in the final intention-to-treat analyses (Figure 2). The final visit of the last randomized patient was performed on January 15, 2020.

Primary endpoint-clinical outcomes: The overall incidence of delirium after PCI in elderly patients was 33.3% (99/297). The incidence of delirium was 27% (40/148) in the Mel group and 39.6% (59/149) in the placebo control group at 7 days after surgery. The incidence of delirium was significantly higher in the placebo group than in the Mel group ($P = 0.02$). After 30 days of follow up, nine patients were not included in the calculation of mortality rate because they were lost to follow up after discharge. The 30-day all-cause mortality rate in the Mel group was 12.2% (18/148), while in the placebo control group, it was 14.1% (21/149); this was not significantly different ($P = 0.02$). (Table 2)

Secondary endpoint: Previous clinical studies found that postoperative hospital stay and hospitalization costs of patients with delirium, compared with those without delirium, were significantly increased, so the present study also compared the average length of hospital stay and hospitalization costs between the two groups. The mean length of

Table 3. Comparison of Secondary endpoint between the two groups

	Placebo	Mel	P-value
Number of patients	149	148	
Hospital stay (day, mean±SD)	13.4±6.6	15.9±9.7	0.01
Hospitalization costs (CNY, mean±SD)	4.7±1.4	5.3±1.8	0.001

stay in the Mel group was 13.4 days, and the mean length of stay in the placebo group was 15.9 days, which was a statistically significant difference between the two groups ($P = 0.01$). The average hospitalization cost of the Mel group was 47,000 RMB, which was significantly lower than the 53,000 RMB in the placebo control group ($P = 0.001$). (Table 3)

Safety evaluation-postoperative complications: There was one case of mild liver dysfunction in the control group and three cases of mild liver dysfunction in the Mel group, which improved after liver protection treatment. No unblinding was necessary during the treatment period, nine patients were lost to follow up after discharge and did not contribute to the mortality statistics, and no instances of shedding cases were found.

DISCUSSION

The present study found that in elderly patients after PCI, prophylactic low-dose Mel orally after surgery can significantly decrease the incidence of postoperative delirium. Mel

supplementation improved sleep after surgery. It also shortened the length of stay in the hospital and decreased hospitalization expenses, while postoperative complications, such as liver dysfunction, were similar.

The overall incidence of postoperative delirium in older patients following PCI was 33.3%, similar to previous reports [Al Tmimi 2020]. Li et al. [Li 2019] also reported that 28.8% of aged individuals with acute ST-segment elevation myocardial infarction developed delirium after primary PCI. Another recent study reported that the 7-day incidence of delirium after PCI in acute coronary syndrome patients accompanied by renal dysfunction was 15.97%. The exact pathogenesis of postoperative delirium in elderly patients after PCI remains unclear. Our previous literature review reported that a variety of factors may induce postoperative delirium [Chen 2020]. (Figure 3) Previous studies have found that delirium is associated with mortality, disability rates, longer hospital stays, poor functional recovery, and long-term cognitive decline in patients older than 70 [Xuan 2018; Pandharipande 2014; Abelha 2013]. In addition, postoperative delirium can aggravate the economic burden on patients and families, affect hospital bed turnover, and prolong hospital stays. Therefore, it is very important to decrease the incidence of perioperative delirium. Recent meta-analyses of the literature based on multicenter randomized controlled studies have failed to identify a safe and effective drug for the prevention or treatment of delirium in critically ill adults [van den Boogaard 2018].

Melatonin is a free radical scavenger and broad-spectrum antioxidant secreted by the pineal gland [Liu 2019] that can not only improve vasospasm and early brain damage but also significantly improve sleep disorders and reduce the incidence of delirium [Han 2020]. Unexpectedly, the anti-delirium role of Mel has always been a controversial issue. Jaiswal et al. [SJ 2019] demonstrated that 3 mg Mel did not reduce the incidence of delirium after endovascular treatment with pulmonary thrombocytes in a randomized controlled trial, and the same study team also demonstrated that Mel did not improve delirium or sleep in patients with severe hospitalization in a prospective randomized controlled study [SJ 2018]. However, Yang et al. [CP 2020] also found that low doses of Mel can decrease the incidence of delirium through a meta-analysis of the literature and prospective randomized controlled studies. However, there was no evidence regarding the effect of Mel on postoperative delirium in elderly patients with PCI.

In the present study, Mel significantly improved the incidence of postoperative delirium in elderly patients after PCI compared with the placebo control group, but it did not improve the 30-day all-cause mortality after PCI. The specific molecular mechanism of the anti-delirium effects after Mel administration in elderly postoperative delirium after PCI may be closely related to its anti-vasospasm effects, improvements in vascular endothelial cell function, anti-neuronal apoptosis, and improvements in cerebral perfusion and sleep quality [Chen 2020]. The study also found that patients' length of stay in the intensive care unit and hospitalization costs were significantly reduced as the incidence of postoperative delirium decreased.

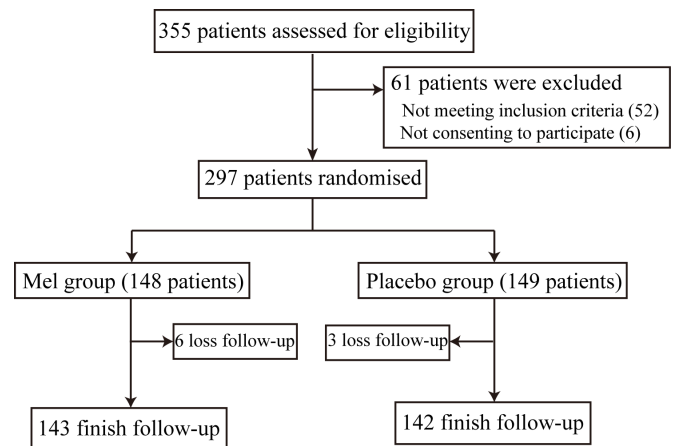


Figure 2. Trial profile

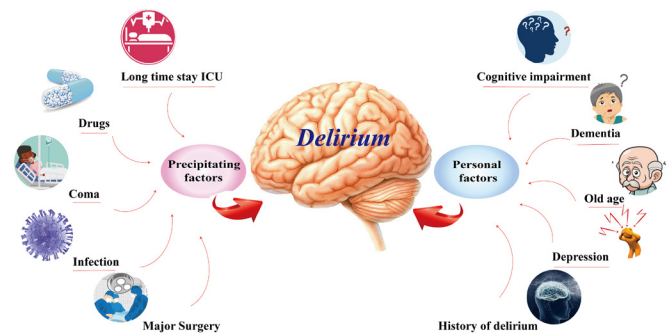


Figure 3. Etiology of delirium (reproduced from our previous study [Chen 2020])

The limitations of this study were as follows:

1. We collected key baseline and outcome data but did not call patients back for study visits for detailed assessments of quality of life or activities of daily living (ADL).
2. All participants were screened and enrolled after ICU admission and did not have baseline delirium assessments with cognitive function assessments.
3. This study used a single dose of Mel. The conventional low dose may not work well.
4. This study did not take into account clinical factors, such as subjective sleep quality, pain, daily prevalence of delirium, and time to extubation.

CONCLUSION

The results from this trial demonstrated that Mel therapy reduces postoperative delirium after PCI. No evidence was found that low-dose Mel increased postoperative complications. Additionally, it significantly decreased hospitalization expenses and hospitalization time. Whether the favorable effects afforded by this novel application of Mel will result in improved long-term outcomes remains unknown. Further

investigation of patients undergoing other operations and the effects of different doses is necessary to fully understand the potential usefulness of Mel in postoperative patients.

ACKNOWLEDGEMENT

The study protocol received ethics committee approval from all participating centers. Written informed consent was obtained from patients whose competence was established by their accurate orientation for time, place, and person, as well as an understanding of the recruiter's description of the trial or otherwise from their next of kin or their legal representative. We would like to acknowledge the technical and language support of Jiangsu Brilliant Biological Technology Co., Ltd.

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