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Original Contribution

The effect of melatonin on early postoperative cognitive decline in elderly patients undergoing hip arthroplasty: A randomized controlled trial☆

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ABSTRACT

Study objective: The purpose of the present study was to investigate whether exogenous melatonin supplementation could ameliorate early postoperative cognitive decline (POCD) in aged patients undergoing hip arthroplasty with spinal anesthesia.
Design: Prospective cohort study.
Setting: Department of Anesthesiology, Jinling Hospital, Nanjing University, Nanjing, China.
Patients: One hundred and thirty–nine patients with ASA I–III, older than 65 yr of age (mean age: 74.5 ± 5.5; gender: male 53 and female 86), scheduled for hip arthroplasty were included in the present study.
Interventions: Patients were randomized to receive 1 mg oral melatonin or placebo daily 1 h before bedtime one day before surgery and for another 5 consecutive days postoperatively.
Measurements: The subject assessment, including Mini–Mental State Examination (MMSE) score, subjective sleep quality, general well–being, postoperative fatigue, and visual analogue scale for pain were evaluated pre–operatively and at days 1, 3, 5, and 7 after surgery.
Main results: The MMSE score in the control group decreased significantly after surgery when compared with its own preoperative value or the melatonin group at days 1, 3, and 5. However, the MMSE score in the melatonin group remained unchanged during the 7 days of monitoring. In addition, significant postoperative impairments of subjective sleep quality, general well–being, and fatigue were found in the control group when compared with the melatonin group.
Conclusion: Peroperative melatonin supplementation might improve early POCD, suggesting restoration of normal circadian function with good sleep quality may be one of the key factors in preventing or treating POCD.

1. Introduction

Postoperative cognitive decline (POCD) is a common complication after major surgeries and affects a wide variety of cognitive domains, including attention, memory, executive function, and speed of information processing [1–3]. A multi–center trial has demonstrated that POCD is present in 25.8% at 1 week and 9.9% at 3 months postoperatively in patients older than 60 yr after non–cardiac surgeries [2]. Accumulating evidence has shown that advanced age is an independent risk factor for the development of POCD [1–3]. The consequence of POCD has gained ongoing public concerns over the last decade because this complication is associated with poor patient outcomes, including increased hospital stay, reduced quality of life, loss of social dependence, and increased mortality [1–4].

The underlying mechanisms leading to POCD remain largely unknown but likely involve a combination of patient, surgical, and anesthetic factors [4,5]. It is well established that the overall sleep loss and sleep fragmentation may have negative impact on cognitive performance [6,7]. Surgery causes sleep disturbances on several levels, including a disrupted sleep pattern [8,9]. It is reported that a significant decrease in rapid eye movement (REM) sleep occurs on the first postoperative night, followed by a profound rebound phenomenon on the second to fourth postoperative night, where REM sleep increases in both intensity and amount [9,10]. In particular, the elderly patient is at a higher risk of developing severe sleep disruption in the postoperative period [4,9,11]. Therefore, improvement of postoperative sleep quality may have a potential benefit to ameliorate POCD.

It has been demonstrated that exogenous melatonin can improve sleep quality by reducing sleep onset latency, increasing sleep

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efficiency, and increasing total sleep duration in healthy subjects [12] and in patients with primary sleep disorders [13]. In addition, melatonin supplementation can improve cognitive dysfunction in healthy men exposed to a psychological stress test, as well as in adults with mild cognitive impairment [14,15]. Based on these findings, we hypothesized that melatonin could have beneficial effects on cognitive dysfunction in aged patients undergoing hip arthroplasty with spinal anesthesia.

2. Materials and methods

2.1. Patients

The study protocol was formally approved by the Institutional Review Board of Jinling Hospital, Nanjing University and written informed consents were obtained from the patients. The study was performed in accordance with the Declaration of Helsinki principles. One hundred and eighty–three patients with ASA I–III, older than 65 yr of age, scheduled for hip arthroplasty were consecutively recruited for the study. Approximately 1–2 days preoperatively, patients were assessed and screened for inclusion. Patients were responded to a questionnaire package including demographic and occupational characteristics, and Pittsburgh Sleep Quality Index. Exclusion criteria included: Mini–Mental State Examination (MMSE) score < 23; allergy to melatonin; chronic sleep disorder; regular shift work; known sleep disorder; history of alcoholism, drug dependence, psychiatric or neurological diseases (Alzheimer's disease, stroke and psychosis, et al.); unwillingness to comply with the protocol or procedures; terminal status or inability to understand the language (Chinese) used. In the present study, we followed the CONSORT diagram, including the screening, randomization, and follow–up of the patients (Fig. 1).

2.2. Study design and melatonin treatment

Patients were randomly assigned using the sealed envelope method to receive either melatonin or placebo. Patients in the melatonin group received 1 mg oral melatonin (Armonia® Retard 1 mg; Nathura, Montecchio Emilia, Italy) daily 1 h before bedtime one day before surgery and for another 5 consecutive days postoperatively. The pharmacy packed the melatonin/placebo in identical, sequentially numbered, sealed boxes. Melatonin used in this study contains a high–purity melatonin preparation (99.9%).

2.3. Measurements

Subject assessment was made by one well trained investigator on the morning one day before surgery and at days 1, 3, 5, and 7 postoperatively. For assessment of perioperative subjective sleep quality, a 100 mm visual analogue scale (VAS) was used, with a higher score indicating poorer habitual sleep quality. For assessment of general well–being, a 100 mm VAS, ranging from extremely well to extreme malaise was used (0 mm = extremely well; 100 mm = extremely malaise). For assessment of postoperative fatigue, a validated 10–point fatigue scale [16] was used (1 = fit; 10 = fatigued). Subject pain was assessed with a 10–cm VAS, where 0 represented “no pain” and 10 represented “most severe pain”.

2.4. Anesthesia and post–operative analgesia

All the subjects had spinal anesthesia at the lumbal$_{2-3}$ or lumbal$_{3-4}$ interspace by employing the needle through–needle technique with a 18–gauge needle. After then, 0.75% bupivacaine (1.5–1.7 ml)–10% glucose (0.2–0.3 ml) mixed solution was given intrathecally via a 25–gauge spinal needle. In addition, all the patients received the same postoperative pain control protocol of patient controlled analgesia (PCA, a constant infusion rate of 2 ml/h with a lock time of 15 min) with fentanyl 12 μg/kg plus ondansetron 16 mg for 2 days.

2.5. Cognitive function measurement

Cognitive function was performed by a well-trained investigator who was blind to the study grouping between 14:00–17:00 pm preoperatively and at days 1, 3, 5, and 7 postoperatively in a quiet room with Chinese version [17]. The Folstein MMSE is a 30–question assessment of cognitive function that evaluates attention and orientation,

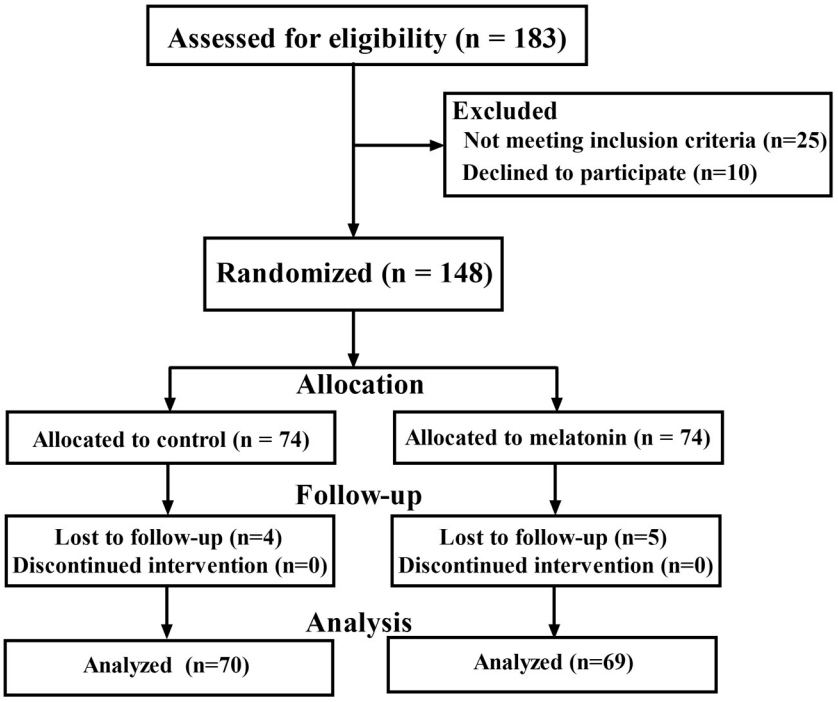

Fig. 1. Study flow diagram showing the flow of participants through each stage of the randomized trial.