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ORIGINAL ARTICLE

Dexmedetomidine reduces postoperative delirium after joint replacement in elderly patients with mild cognitive impairment

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Abstract
Background and aims Postoperative delirium (POD) is a common and serious surgical complication among the elderly, especially in those with amnestic mild cognitive impairment (aMCI). Dexmedetomidine (DEX) is neuroprotective for delirium. In this study, we determined the effect of intravenously administered DEX during general anesthesia on POD in elderly aMCI patients undergoing elective hip joint or knee joint or shoulder joint replacement surgery.
Methods This was a prospective, randomized parallel-group study of aMCI ($n = 80$) and normal elderly patients ($n = 120$). Prior to surgery, all subjects underwent neuropsychological assessment and were assigned to one of four groups: the aMCI DEX group (MD group, $n = 40$), the aMCI normal saline group (MN group, $n = 40$), the control DEX group (CD group, $n = 60$), and the control normal saline group (CN group, $n = 60$). The confusion assessment method was used to screen POD on postoperative days 1, 3, and 7.
Results We found patients age was positively correlated with POD incidence in the MN group ($p < 0.05$) but not in the CN group ($p < 0.05$). DEX treatment significantly decreased POD incidence in both control and aMCI groups relative to their respective placebo groups (all $p < 0.05$). The fraction of patients whose normal cognitive function was not restored by day 7 after surgery was significantly higher in the MN group than the MD and CN groups (all $p < 0.05$).
Conclusions These findings suggested that DEX treatment during surgery significantly reduced POD incidence in both normal and aMCI elderly patients, suggesting that it may be an effective option for the prevention of POD.

Keywords Delirium · Surgery · Amnestic mild cognitive impairment · Dexmedetomidine

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Introduction

Delirium is an acute state of confusion characterized by a reduction in the ability to focus, sustain, or shift attention and cognitive changes, including memory loss, disorientation, language disturbance, and perceptual disturbance [1]. Although there is variability in the reported prevalence of delirium in similar settings [2], approximately 20 % of hospitalized patients 65 years and older develop postoperative delirium (POD), accounting for 12.5 million cases each year [3]. POD is a frequent and serious postoperative complication in the elderly, often leading to poor outcomes, including increased mortality, increased length of hospital stay, functional disability, placement in long-term care institutions, and increased hospitalization costs [4, 5]. POD develops within hours to days, and symptoms of POD tend to fluctuate over the course of the day [6]. Although the causes of POD have not yet been identified, several factors, such as advanced age, sex, stroke, use of narcotic analgesics, poor physical condition, alcoholism [7], subjective memory complaints, pre-existing cognitive impairment (Pre-CI) [8], and mild cognitive impairment (MCI), have been linked to increased POD risk.

In a study of nondemented community dwelling elderly admitted to the hospital for acute delirium, 38 % of patients had dementia 2 years later [9]. POD is common in the elderly after surgical repair of hip fractures [10], where 50 % of elderly patients developed POD, and 29 % developed severe delirium [11]. Similarly, in nondemented femoral neck fracture patients, an episode of POD was linked to the development of dementia, higher mortality rate, longer hospitalization, poorer functional recovery [12], and decreased likelihood of returning to previous independent living arrangements [13]. In these studies, cognitive ability prior to the surgery was not established, and MCI patients were usually considered normal. One study found that 20 % of elderly subjects undergoing elective total hip joint replacement surgery exhibited PreCI, and of those, 22 % had amnestic MCI (aMCI) [14]. Therefore, it is very important to establish baseline cognitive ability when assessing POD, and cognitive evaluation should be included in the preoperative assessment [15].

MCI refers to mild impairments in cognitive function with intact memory performance, and it may be a transitional stage between normal aging and the development of Alzheimer's disease (AD) [16]. More specifically, aMCI is a strong risk factor for the progression to AD and dementia, with an annual conversion rate of 10–15 % for both [17, 18]. Consistent with this, there is evidence that subjects with aMCI already exhibit AD pathology [19]. We previously showed that progress of aMCI was accelerated 2 years after surgery and sevoflurane anesthesia, but not after propofol anesthesia. However, in that study we did not determine the relationship between POD and disease progression.

Dexmedetomidine (DEX), a highly selective α2-receptor agonist, provides excellent sedation and analgesia with minimal respiratory depression [20], greater patient satisfaction, and less need for opioids [21, 22]. DEX may be neuroprotective, and its use has been linked to decreased postoperative delirium, stress, and inflammatory responses [23–26], shortened duration of postoperative delirium [27], and increased postoperative cognitive function [25, 26, 28]. In the present study, we evaluated the effect of intravenously administered DEX during general anesthesia on POD in elderly patients with aMCI undergoing elective hip joint or knee joint or shoulder joint replacement surgery.

Materials and methods

Patients

The study protocol was approved by the Institutional Review Board and the Ethics Committee of Beijing Military General Hospital, and written informed consent was obtained from each patient prior to the start of the study. The clinical trial registration number was ChiCTR-ICC-15006276. aMCI ($n = 80$) and normal elderly (65–80 years old) patients ($n = 120$, control patients) who underwent a total hip joint or knee joint or shoulder joint replacement surgery with general anesthesia between September 2014 and May 2015, with an American Society of Anesthesiologists physical status II to III were enrolled in the study. A computer-generated random number scheme was used to assign the 200 patients to one of four groups: the aMCI DEX group (MD group, $n = 40$), the aMCI normal saline group (MN group, $n = 40$), the control DEX group (CD group, $n = 60$), and the control normal saline group (CN group, $n = 60$). Before surgery, all subjects underwent a neuropsychological assessment by a single doctor who was not involved in anesthesia or surgery. The drugs were prepared by one nurse who was not involved in anesthesia or surgery. Both patients and anesthesiologists were blinded to preoperative cognitive function and whether DEX or placebo was administered during surgery. Patients were excluded from the study based on the presence of one of the following conditions: neurological diseases that may affect cognitive function (e.g., subdural hematoma, vascular dementia, frontotemporal dementia, hypothyroidism, alcoholic dementia, vitamin B12 deficiency, and encephalitis), hypoxic pulmonary disease, and perioperative serious cardiopulmonary complications [29].

aMCI was diagnosed clinically with the following criteria: subjective memory complaint (preferably qualified by an informant), an objectively demonstrable memory impairment (e.g., performance 1.5 standard deviations below age-, sex-, and education-matched peers), Clinical Dementia Rating (CDR) score of 0.5, activities of daily living (ADL) score ≤26, a Mini-Mental State Examination (MMSE) score ≤27 (17–27 for illiterates, 20–27 for patients with ≤6 years education, and 24–27 for those with >6 years education), and a Montreal Cognitive Assessment (MoCA) score in the range of 15–24 (indicating no dementia and below the threshold for diagnosis of AD) [29].

Confusion assessment method (CAM) was used to screen POD. The CAM algorithm consists of four clinical criteria: (1) acute onset and fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. For delirium, both the first and the second criteria must be present plus either the third or the fourth criteria or both [30].

Anesthesia procedure

Patients were not medicated prior to surgery. Upon their arrival to the operating room, patients were monitored with invasive blood pressure, an electrocardiogram, a pulse oximeter, and bispectral index (BIS). Anesthetic management was standardized across patients. Midazolam

(0.04 mg/kg), etomidate (2 mg/kg), fentanyl (3 µg/kg), and rocuronium (0.6 mg/kg) were used to insert the laryngeal mask (i-gel, Intersurgical Ltd, Wokingham, UK). After induction, patients received a bolus fentanyl infusion (1 µg/kg) and continuous infusion with a syringe pump of propofol (4–6 mg/kg/h) and remifentanil (8–12 µg/kg/h). In the DEX groups, a continuous infusion of DEX at 0.2–0.4 µg/kg/h, without an initial dose, was administered throughout the duration of the surgery. In the control groups, a placebo infusion of normal saline was given. During surgery, the infusion rates of propofol, remifentanil, and DEX were titrated to maintain BIS values between 40 and 50 and changes in mean arterial pressure (MAP) and heart rate (HR) ±20 % of preanesthetic baseline levels. During surgery, patients were given lactated ringer's solution and hetastarch (5–8 mL/kg) every hour. If hemoglobin levels fell under 80 g/L, concentrated red blood cells were infused. A change in MAP > 20 % below baseline level was corrected with ephedrine. Propofol and remifentanil were discontinued at 5 min, and DEX or placebo was stopped 20 min before the end of surgery. Drugs were not used to reverse the neuromuscular blockade. After restoration of normal breathing and consciousness, the laryngeal mask was removed. A single bolus of fentanyl (0.08 µg/kg) and ondansetron (0.1 mg/kg) was given, and continuous infusion of fentanyl (0.3 µg/kg/h) and ondansetron (12 µg/kg/h) was administered over a 15 min interval for postoperative pain relief. Nonsteroidal anti-inflammatory agent parecoxib was injected intravenously when the visual analogue scale (VAS) was higher than three.

Clinical evaluation

To differentiate aMCI, all the patients prior to surgery were subjected to neuropsychological assessments, including MMSE, MoCA, ADL, and CDR. For postoperative assessment, CAM was used to identify POD on days 1, 3, and 7 after surgery. If patients were normal at 3 days, no follow-up was necessary.

Statistical analysis

Statistical analyses were performed using the SPSS 10.0 software package (SPSS Inc, Chicago, IL). All the data for continuous variables (age, weight, duration of surgery, HR, MAP, SpO2, and MMSE) are shown as mean ± standard deviation. A Pearson χ^2 test was used to detect differences in sex, age, diabetes, POD, and POD duration days between groups. When there were less than 40 samples, exact probabilities in a fourfold table were used. Scheffe post hoc test was used to compare differences in POD duration days between groups. To compare the four groups, one-way analysis of variance (ANOVA) was performed with a post hoc least significant difference test. A Spearman's rank correlation test was used to calculate correlation between age and POD, and the linear trend test was used to analyze bidirectional order grouping data. $p < 0.05$ was considered statistically significant.

Results

Subjects who did not complete the study, including one patient in the MD group and two patients in the CN group, were sent to the intensive care unit because of delays in recovery. All other patients recovered from anesthesia within 15 min after the end of surgery (Fig. 1).

The levels of HR, MAP, and $EtCO_2$ during surgery were maintained within ±20 % of preoperative levels. As summarized in Table 1, sex, age, age composition, weight, duration of surgery, and education did not differ significantly among the four groups. The number of diabetics in aMCI group was much more than the normal group (44/78 and 39/118, $p < 0.01$).

As shown in Table 2, the amount of propofol and remifentanil used during anesthesia in the MD group was significantly less than the MN group in two age categories ($p < 0.01$). Relative to the CN group, the usage of propofol and remifentanil was significantly less than the CD group ($p < 0.01$).

As shown in Table 3, MMSE scores before surgery were not significantly different between the MD group and the MN group, and between the CD group and CN group. However, MMSE scores were significantly lower in the aMCI groups than the normal groups (all $p < 0.01$). MoCA and ADL scores were not significantly different among the four groups (all $p > 0.05$).

Patients were stratified into two age categories (65–75 and ≥75 years) to investigate the correlation between age and POD incidence (Table 4). In the MN group, subject's age correlated linearly with the incidence of POD ($p < 0.05$), while not in the CN group. Relative to the CN group, the incidences of POD were significantly higher in 65–75-year-old and ≥75-year-old patients in the MN group (all $p < 0.05$) and significantly decreased at 65–75-year-old and ≥75-year-old in the CD group (all $p < 0.05$). Relative to the MN group, both age categories in the MD group exhibited significantly decreased incidence of POD (all $p < 0.05$). For both age groups, there was no significant difference between the MD and CN groups.

Cognitive function was not restored in some patients by postoperative day 7, including 13 patients (13/25) in the MN group, 2 patients (2/10) in the MD group, and 3 patients (3/18) in the CN group. All POD patients in the CD group recovered to normal cognitive function by

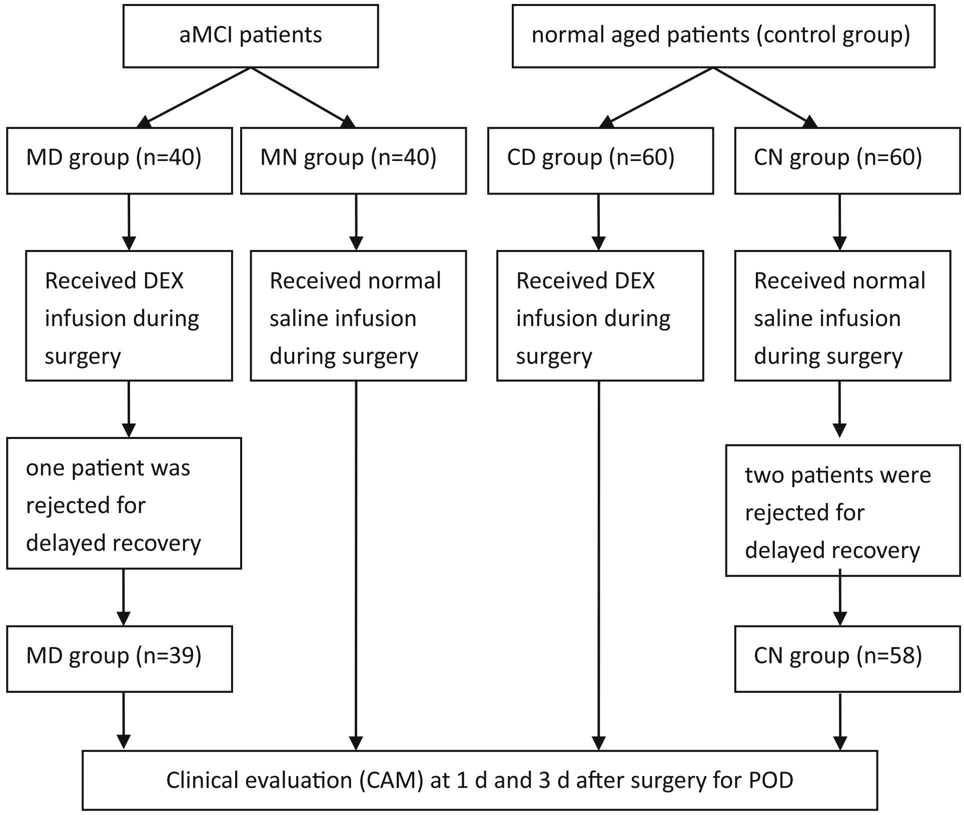

Fig. 1 Schematic drawing of the experimental design

Table 1 Patient data

Variables	aMCI+DEX (MD, $n = 39$)	aMCI+NS (MN, $n = 40$)	Control+DEX (CD, $n = 60$)	Control+NS (CN, $n = 58$)	p value
Sex (M/F)	18/21	23/17	26/34	29/29	0.557
Age (yr)	72.84 ± 8.17	75.25 ± 7.76	71.23 ± 8.08	72.81 ± 9.22	0.155
65–75 (n)	31	30	42	39	0.565
≥75 (n)	8	10	18	19	
Weight (kg)	59.39 ± 8.42	61.37 ± 9.09	57.76 ± 10.36	60.77 ± 7.52	0.170
Duration of surgery (h)	1.42 ± 0.30	1.31 ± 0.48	1.37 ± 0.59	1.56 ± 0.54	0.079
Education (year)	5.27 ± 3.85	4.58 ± 2.13	5.24 ± 2.36	5.43 ± 3.29	0.549
Complications					
Coronary heart disease (n)	8	10	6	9	0.224
Diabetes	22	26	19	14	0.000
Hypertension	20	22	19	20	0.0537

Data are expressed as mean ± standard deviation

postoperative day 7. The ratio of POD patients who did recover by day 7 to total POD patients was significantly greater in the MN group than the MD and CD groups (all $p < 0.05$), and the ratio of the MN group was not significantly different than the CN group.

These data suggested that age is not a risk factor for POD in normal elderly patients, whereas it is for aMCI patients. DEX administered during surgery significantly reduced the usage of propofol and remifenanil, the incidence of POD in aMCI and normal patients, and the duration of POD days.

Discussion

In the present study, we determined whether administration of DEX improved outcomes in elderly patients with aMCI who underwent elective hip joint or knee joint or shoulder

Table 2 The total dose of anesthetics during surgery

Variables	aMCI+DEX (MD, $n = 39$)		aMCI+NS (MN, $n = 40$)		Control+DEX (CD, $n = 60$)		Control+NS (CN, $n = 58$)	
	65–75 (year)	≥75 (year)	65–75 (year)	≥75 (year)	65–75 (year)	≥75 (year)	65–75 (year)	≥75 (year)
Propofol (mg)	288.75 ± 43.90*	275.31 ± 51.97*	489.42 ± 54.58	468.44 ± 43.86	274.01 ± 46.95#	260.26 ± 43.93#	531.25 ± 43.90	493.24 ± 56.37
Remifentanil (μg)	675.75 ± 43.62	643.12 ± 48.16	876.02 ± 63.61	822.41 ± 61.90	641.19 ± 51.97	659.24 ± 44.59	918.00 ± 74.78	869.83 ± 75.91

* $p < 0.01$ versus aMCI+NS at two age categories, # versus Control+NS at two age categories

joint replacement surgery under general anesthesia. Older age in aMCI patients was linked with increased POD, whereas POD occurrence did not increase with aging in normal elderly patients. DEX treatment significantly reduced the incidence of POD in both normal and aMCI elderly patients.

Delirium is the most common form of acute brain dysfunction in critically ill patients, and it often goes undetected. We found that the incidence of POD in aMCI patients was higher than in normal elderly patients, suggesting that preoperative cognitive impairment, such as lower MMSE scores and subjective memory complaints, is closely related to the manifestation of POD. To identify patients at risk of developing POD, preoperative assessment by MMSE and direct questions about memory impairment is necessary [15] especially for identification of aMCI patients.

aMCI patients exhibit a broad spectrum of morphological brain changes and pathological characteristics typical of AD like anomalously phosphorylated (p) tau and Aβ fragments in the cerebrospinal fluid (CSF) [31]. aMCI may represent in some individuals a predementia stage of AD, with a population conversion rate to dementia of 10–15 % per year, independent of any effects of anesthesia and surgery [32]. However, there is evidence linking anesthesia and surgery to exacerbation of AD pathologic mechanisms, further augmenting the conversion rate of aMCI to AD [33]. We had found previously that inhaled sevoflurane accelerated the progression of aMCI to progressive MCI after 2 years [29]. Therefore, it is important to neuropsychologically evaluate patients at risk, to identify them prior to surgery and to monitor them closely to prevent POD occurrence. Meanwhile, there was a relationship between aging and POD in aMCI patients but not normal elderly patients, demonstrating that age in aMCI patients is an important predictor of POD incidence.

Previously, DEX treatment significantly reduced the incidence of POD in critically ill patients and those undergoing cardiac surgery with cardiopulmonary bypass [34]. DEX also improved the anesthetic/surgery-induced POCD, attenuated inflammatory response, reduced neuronal apoptosis in hippocampus [35], and decreased the need for benzodiazepines and opioids [36]. Moreover, DEX does not affect the cholinergic system, a major system implicated in cognitive function and the development of delirium. For intensive care unit patients, DEX is a promising agent not only for prevention but also for the treatment of delirium in critically ill patients [37]. Here, administration of DEX during hip joint or knee joint or shoulder joint replacement surgery (anesthesia with propofol and remifentanil) reduced the incidence of POD in aMCI and normal patients at 65–75 years and >75 years old.

Table 3 Preoperative clinical evaluations

Variables	aMCI+DEX (MD, $n = 39$)	aMCI+NS (MN, $n = 40$)	Control+DEX (CD, $n = 60$)	Control+NS (CN, $n = 58$)
MMSE	23.26 ± 2.66*	$22.43 \pm 2.60^{\#}$	26.17 ± 3.52	25.39 ± 2.41
MoCA	19.82 ± 4.62	20.65 ± 5.14	20.30 ± 3.23	18.57 ± 3.06
ADL	19.56 ± 4.18	21.61 ± 2.80	21.53 ± 3.81	20.02 ± 3.74
CDR	0.5	0.5	0.5	0.5

* $p < 0.01$ versus Control+DEX, # $p < 0.01$ versus Control+NS

Table 4 Correlation between age and POD incidence POD incidence and duration days in two age categories for each group

Variables	aMCI+DEX (MD, $n = 39$)		aMCI+NS (MN, $n = 40$)		Control+DEX (CD, $n = 60$)		Control+NS (CN, $n = 58$)	
	65–75 (year)	≥75 (year)	65–75 (year)	≥75 (year)	65–75 (year)	≥75 (year)	65–75 (year)	≥75 (year)
POD (n, %)	7/31 (22.58 %)$^{\%}$	3/8 (37.5 %)$^{\wedge}$	16/30 (43.33 %)*	9/10 (90 %)$^{\#}$	4/42 (11.90 %)*	1/18 (16.67 %)$^{\#}$	11/39 (30.77 %)	7/19 (36.84 %)
Spearman correlation			$p = 0.038$				$p = 0.505$	
Linear regression			$p = 0.038$				$p = 0.505$	
Duration days (n)								
1 day	3	2	5	1	2		6	3
3 days	3		4	2	2	1	4	2
7 days	1	1	7	6			1	2

* $p < 0.01$ versus Control+NS, % $p < 0.01$ versus aMCI+NS at 65–75 years old; # $p < 0.01$ versus Control+NS, ^ $p < 0.01$ versus aMCI+NS at ≥ 75 years old

Increased body mass index, obesity, impaired glucose tolerance, and type 2 diabetes can significantly increase the incidence of AD and anticipate the age of onset of AD [38]. Absence of insulin in the brain was shown to promote pathological changes and behavioral abnormalities similar to AD and to increase severity of existing AD pathologic lesions [39]. Aβ in AD is toxic to A and B cells in the pancreas, further aggravating existing hormone disorders [40]. aMCI may be an early stage of AD, and we found that the incidence of diabetes in patients with aMCI was significantly higher than normal elderly. Therefore, for those elderly patients with diabetes, especially those with aMCI, preoperative cognitive function should be evaluated and presence of POD monitored.

Management of pain in elderly is an important factor for the development of POD. Avoiding opioids or using very low doses of opioids has been linked with increased risk for delirium. Indeed, cognitively intact patients with undertreated pain were nine times more likely to develop delirium than those patients whose pain was adequately treated, especially in frail older adults [41]. In this study, postoperative pain was alleviated appropriately and in a timely manner, therefore, it was unlikely a factor that affected the conclusions of the study.

POD is not always temporary and can often result in persistent functional and cognitive losses in elderly hospitalized patients [42]. Prolonged duration of POD is an independent risk factor for the development of long-term postoperative cognitive dysfunction (POCD) [37]. In our study, some POD patients did not recover to preoperative cognitive levels by day 7 after surgery (the last day we evaluated patients), and this impairment may be long lasting.

There are a few limitations of our study. First, we did not observe the incidence of POCD after surgery. Second, we did not investigate the relationship between POD and POCD. Third, because of the time restraints of our study, we were unable to investigate the relationship between POD and conversion ratio of dementia. In the future, more long-term studies should be performed to address these important issues.

In conclusion, we found that in aMCI patients, the occurrence of POD was related to aging after total hip joint or knee joint or shoulder joint replacement surgery under general anesthesia. Administration of DEX during surgery was associated with a significant reduction in POD incidence in both normal and aMCI elderly patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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