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Original Article

Effects of dexmedetomidine for postoperative delirium after joint replacement in elderly patients: a randomized, double-blind, and placebo-controlled trial

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Abstract: *Background:* Experimental evidence has indicated the benefits of dexmedetomidine for the treatment of postoperative delirium. Previously clinical trials have had no definite conclusions concerning dexmedetomidine on delirium, while some studies have shown it can reduce delirium. One study showed it cannot improve outcomes. The present study, therefore, explored whether acute dexmedetomidine treatment could reduce incidence of delirium and improve clinical outcomes. *Methods:* This was a randomized, double-blind, and placebo-controlled trial in three hospitals in Jiangsu and Anhui, China. This study enrolled patients aged more than 60 years old, admitted to Intensive Care Units after joint replacement surgery, with informed consent. A computer-generated randomization sequence (in a 1:1 ratio) was used to randomly assign patients to receive either dexmedetomidine (0.1 μg/kg per hour, from intensive care unit admission on the day of surgery) or placebos once daily for up to 3 days. Participants, care providers, and investigators were all masked to group assignment. The primary endpoint was incidence of delirium, assessed twice daily with the Confusion Assessment Method during the first 7 postoperative days. Analyses were performed by intention-to-treat and safety populations. *Results:* Between August 1, 2015, and August 1, 2017, 545 patients were assessed. A total of 453 were randomly assigned to receive either placebo (n=226) or dexmedetomidine (n=227). Incidence of postoperative delirium was significantly lower in the dexmedetomidine group (30 [13.2%] of 227 patients) than the placebo group (64 [28.3%] of 226 patients (Odds ratio [OR]=0.385, 95% CI 0.238-0.624; p<0.0001). Regarding safety, incidence of hypertension was higher with placebos (32 [14.2%] of 226 patients) than with dexmedetomidine (18 [7.9%] of 227 patients; OR=0.522, 95% CI 0.284-0.961; p=0.034). Occurrence of hypotension and bradycardia did not differ between groups. *Conclusion:* The current study suggests that acute dexmedetomidine treatment can reduce incidence of delirium after joint replacement. However, no evidence was found that dexmedetomidine can improve clinical outcomes. The therapy was safe. Further investigation is necessary to fully understand the potential usefulness of dexmedetomidine in older patients.

Keywords: Dexmedetomidine, joint replacement, delirium

Introduction

Delirium is a common, life-threatening, and often preventable clinical complication in elderly patients. Inouye [1] reported that postoperative delirium occurs in 11-51% of patients after surgery, especially higher in older patients after joint replacement surgery. Delirium has been associated with increased mortality, morbidity, prolonged hospital stays, worse functional recovery, and decreased long-term cognitive function [1-5]. In the United States, more than 2.6 million adults, older than 65 years, each year develop delirium, accounting for an estimated more than $164 billion in annual health care expenditures [1]. Siddiqi [5] reported that around 30-40% of delirium cases are thought to be preventable. Though ongoing research has examined interventions that may prevent and/or treat delirium, minimizing the influence of risk factors during critical illness, no conclusive studies have supported an agent that was consistently efficacious.

Dexmedetomidine is a highly selective α2 adrenoreceptor agonist that provides sedation and analgesic effects with minimal respiratory depression [6]. Dexmedetomidine is mostly used in the Intensive Care Unit (ICU) for decreased prevalence of delirium, especially for decreas-

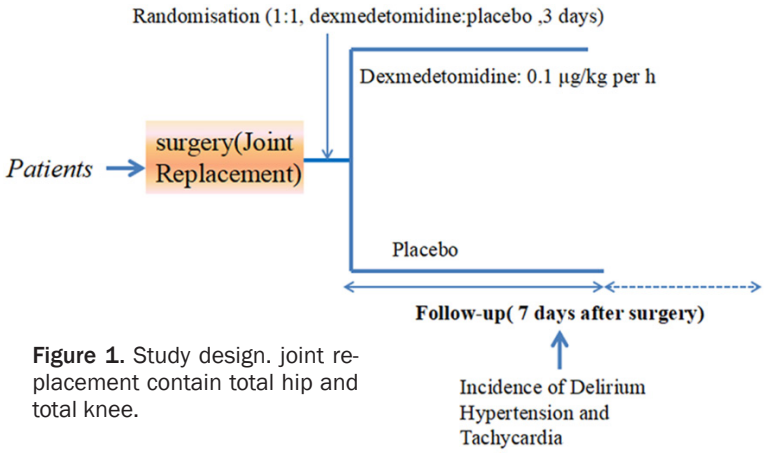

Figure 1. Study design. joint replacement contain total hip and total knee.

ing delirium in mechanically ventilated adult patients in the ICU [2]. Some previous studies have shown that dexmedetomidine reduces agitation in pediatric patients during recovery from general anesthesia and shortens the course of patient delirium after cardiac surgery [2, 7-9]. Another plausible explanation has suggested that dexmedetomidine does not prevent occurrence of delirium [11]. There is a lack of proof from randomized controlled studies after joint replacement in elderly patients. Therefore, it is not clear whether dexmedetomidine has preventive effects against delirium. The present study, therefore, explored whether acute dexmedetomidine treatment could reduce postoperative delirium and improve clinical outcomes after joint replacement.

Methods

Study design

This was a randomized, double-blind, and parallel arm placebo controlled trial of 3 institutions in Jiangsu and Anhui, China, between August 1, 2015, and August 1, 2017. Anhui Medical University Affiliated Wuxi Clinical college (101st Hospital of PLA), Wuxi Huishan People's Hospital in Jiangsu, and Hefei Second People's Hospital in Anhui, China, were included. The study was designed to assess the superiority of intervention. The study protocol was approved by the Anhui Medical University Affiliated Wuxi Clinical College Clinical Research Ethics Committees (2015-YXLL-003). 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 (**Appendix**).

Patients were randomly assigned (1:1) to receive 0.1 μg/kg per hour of dexmedetomidine or placebos within 3 days after joint replacement surgery (**Figure 1**). Dexmedetomidine or placebos were administered via intravenous injections for up to 3 days after joint replacement surgery. Final follow-up was 30 days after surgery.

Study patients

Eligible patients were more than 60 years old with joint replacement surgery in ICU. Inclusion criteria were as follows: (1) Aged more than 60 years; (2) Could be randomized and received dexmedetomidine or placebo within 8 hours after surgery; and (3) Joint replacement surgery under general anesthesia and were admitted to the ICU. Exclusion criteria were as follows: (1) Unsalvageable patients likely on admission; (2) High cholesterol combined with diabetes; (3) Brain injury or neurosurgery; (4) Severe sinus bradycardia; (5) Sick sinus syndrome; (6) Neurologic disease; (7) Abnormal liver enzymes, patients with rhabdomyolysis, and myopathy; (8) Patients with a history of mental illness and epilepsy; (9) Patients with severe lung disease and multiple organ dysfunction; and (10) Researchers found other reasons.

Randomization and masking

Permuted-block randomization was performed using a computer system with an allocation list generated 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. Results of randomization were sealed in sequentially numbered envelopes and stored at the site of investigation until the end of the study. During the study period, all included patients were randomly assigned to

receive either dexmedetomidine (0.1 μg/kg per h, 3 days) or placebos (normal saline). A study nurse administered the study drugs according to the randomization sequence. Both the study members and patients were blinded to the study drug allocation. If an emergency occurred, like severe hepatic failure, then two experts could request unmasking of the treatment allocation or adjust or interrupt study drug if necessary. All situations were documented.

Patient demographics, medical histories, and relevant investigation results were collected.

Procedures

No premedication was administered. All patients underwent a standard preoperative evaluation and were given an American Society of Anesthesiologists (ASA) classification based on their medical comorbidities [12]. All patients received the same general anesthesia protocol. Intravenous (IV) midazolam (1 mg-2 mg) and fentanyl (50 mcg-100 mcg) were given as preoperative sedation and anesthesia was maintained with 3 to 6 mcg/kg of IV fentanyl [13]. All patients were routinely monitored with electrocardiography (ECG), non-invasive blood pressure, pulse oximetry (SpO2), and Bispectral index (BIS). Radial arterial pressure and central venous pressures were monitored as necessary.

After surgery, patients were admitted to the ICU and all patients received the same management. Patients in the treatment group received 0.1 μg/kg per hour of dexmedetomidine as a continuous intravenous infusion (usually started within 1 hour after ICU admission, maintain 3 days), while the placebo group received equal normal saline. During sedation, patients were extubated when they met the following criteria: arterial pressure (MAP) and heart rate (HR) >20% of preanesthetic baseline levels and a level of consciousness associated with reflexes that protect the airway and adequate gas exchange during a spontaneous breathing trial [11].

Study drugs (dexmedetomidine) were provided as clear aqueous solutions in the same 3 mL bottles (Jiangsu Hengrui Medicine Co, Ltd, Jiangsu, China). They were dispensed according to the randomization results by a pharmacist that did not participate in the rest of the study. Study drugs were diluted with normal saline to 50 mL before administration.

Outcome assessment

All clinical and imaging data were assessed by a masked independent diagnostic and assessment committee. This committee included two researchers that were trained before the study and were not involved in the clinical care of patients. The primary endpoint was incidence of delirium in the first 7 days after surgery. The first postoperative delirium was evaluated around 24 hours after surgery and evaluated twice daily (from 6 to 8 am and from 6 to 8 pm) [11, 14]. Delirium was assessment by Confusion Assessment Method (CAM) and the CAM for the Intensive Care Unit (CAM-ICU). Both 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 [14]. Immediately before assessing delirium, sedation or agitation was assessed using RASS. If the patient was too deeply sedated or unarousable (RASS -4 or -5), delirium assessment was aborted and the patient was recorded as comatose. If RASS was greater than -4 (-3 to +4), delirium was assessed by use of the CAM-ICU. Patients with delirium were classified into three motoric subtypes. Hyperactive delirium was defined when RASS was consistently positive (+1 to +4). Hypoactive delirium was defined when RASS was consistently neutral or negative (-3 to 0). Mixed delirium was defined when some RASS scores were positive (+1 to +4) and some RASS scores were neutral or negative (-3 to 0). For patients that were discharged or died within 7 days after surgery, results of the last delirium assessment were considered the results of the missing data. These patients were excluded when calculating daily prevalence of delirium in a post-hoc analysis [11].

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

Dexmedetomidine related adverse events assessment

The most common adverse events included hypotension, bradycardia, and hypoxemia. These were defined as systolic blood pressure, heart rate, and pulse oxygen saturation decreases of more than 20% from baseline.

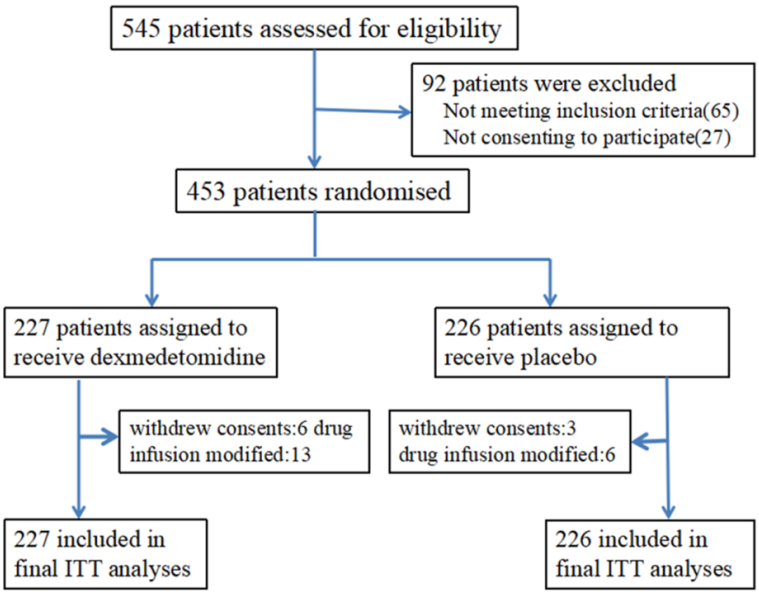

Figure 2. Trial profile. ITT analyses included all randomized patients in the groups to which they were randomly assigned. ITT=intention-to-treat.

Statistical analysis

Based on previous data, it was estimated that 400 patients would be required to confirm these effects with an α of 5% and 80% power [15]. Further assuming a 10% loss to follow-up, 453 patients were enrolled. 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.

This study described the incidence and relative risk reduction of dichotomous variables for the dexmedetomidine-treated group relative to the placebo group, with corresponding 95% CIs. Demographics and safety data are reported as descriptive statistics (means and standard deviation). Categorical variables were analyzed with the χ^2 test, continuity correction χ^2 test, or likelihood ratio χ^2 test. Numeric variables were analyzed by use of an unpaired t-test or Mann-Whitney U-test. Differences (and 95% CI for the differences) between two medians was calculated with the Hodges-Lehmann estimator.

This study did not perform interim analysis. Statistical analyses were done on SPSS 14.0 software (SPSS, Chicago, IL) with two-tailed tests as appropriate. *P* values less than 0.05 indicate statistical significance. The Clinical Research Ethics Committee from Anhui Medical University, Wuxi clinical college (101st Hospital of PLA), was involved in overseeing the data.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors were provided with the full set of statistical tables and figures resulting from the trial data analysis. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between August 1, 2015, and August 1, 2017, 545 patients were assessed. A total of 453 were randomly assigned to receive either placebos (n= 226) or dexmedetomidine (n= 227) (**Figure 2**). There were no lapses in the blinding during the study period. Baseline characteristics of patients showed no statistical significance between the dexmedetomidine and placebo groups (**Table 1**). During the study period, 9 patients withdrew consent (3 in the control group and 6 in the dexmedetomidine group) and drug infusion was modified in 19 patients (6 in the control group and 13 in the dexmedetomidine group) because of adverse events. All patients were included in the final intention-to-treat analyses (**Figure 2**). The final visit of the last randomized patient was done on Aug 28, 2017.

Demographic and clinical data

Patient demographics and baseline characteristics were similar between the dexmedetomidine and placebo groups (**Table 1**). Most of the patients were women. The percentage of patients that required intraoperative blood transfusions was less in the dexmedetomidine group than in the placebo group (**Table 1**). After randomization, a similar proportion of patients received supplemental sedation in both groups. The duration of anesthesia was similar in the two groups. All patients received general anesthesia in the two groups.

Primary endpoint-clinical outcomes

Incidence of delirium during the first 7 postoperative days was 30 (13.2%) of 227 patients in

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

	Placebo group	Atorvastatin group	*P* value
Number of patients	226	227	
Age			0.63
Mean ± SD	66.9±5.1	66.6±7.5	
Gender			0.61
Male	101 (44.7%)	96 (42.3%)	
Female	125 (55.3%)	131 (57.7%)	
History of hypertension			0.21
Yes	69 (30.5%)	82 (36.1%)	
No	157 (69.5%)	145 (63.9%)	
Nicotine use			0.40
Yes	52 (23.0%)	60 (26.4%)	
No	174 (77.0%)	167 (73.6%)	
Type of surgery			0.67
Total hip	126 (55.8%)	131 (57.7%)	
Total knee	100 (44.2%)	96 (42.3%)	
Duration of anesthesia (min)	2.2±0.3	2.2±0.4	0.58
Blood transfusion during surgery			
Yes	20 (8.8%)	25 (11.0%)	0.44
No	206 (91.2%)	202 (89.0%)	
Intraoperative medication			>0.05
Midazolam	119 (52.7%)	135 (59.5%)	
Fentanyl	226 (100%)	227 (100%)	
Propofol	226 (100%)	227 (100%)	
Atropine	25 (11.1%)	31 (13.7%)	
Postoperative analgesics first 7 days			>0.05
Diclofenac sodium	84 (37.2%)	79 (34.8%)	
Diclofenac sodium (mg)*	270±109	268±120	
Morphine	52 (23.0%)	57 (25.1%)	
Morphine (mg)	21.4±7.6	23.2±10.3	
Midazolam	18 (8.0%)	13 (5.7%)	
Midazolam (mg)	38.0±11.1	32.8±5.0	

*The mean dosage among patients that had received the drugs.

the dexmedetomidine group and occurred in 64 (28.3%) of 226 patients; (OR=0.385, 95% CI 0.238-0.624; p<0.0001, **Figure 3**). Per-protocol analysis demonstrated a significant reduction in incidence of delirium between the two groups (62 [28.2%] of 220 patients given placebo vs 26 [12.1%] of 214 patients given dexmedetomidine, OR=0.352; 95% CI 0.213-0.584, p<0.0001, **Figure 3**).

Secondary endpoint

Previous studies have found that hospitalization time and hospitalization expenses significantly increased in delirium patients, compared to others without delirium. Thus, the present study also compared differences between the two groups in hospitalization time and hospitalization expenses. Hospitalization time in the placebo group was significantly increased, compared to the dexmedetomidine group (15.4±4.2 vs 16.5±5.5, P= 0.013, **Figure 4A**). Similarly, hospitalization expenses in the placebo group were significantly higher than the dexmedetomidine group (4.2±0.9 vs 4.5±1.0, P=0.001, **Figure 4B**).

Safety evaluation-postoperative complications

Event rates for each of the individual components of the primary composite endpoints are shown in **Figure 5**. Occurrence of postoperative hypertension was lower in the dexmedetomidine group than in the placebo group (**Figure 5**, 7.9% vs 14.2%, P=0.034, OR=0.522, 95% CI 0.284-0.961). Occurrence of hypotension in the placebo group and dexmedetomidine group showed no differences (**Figure 5**, 8.4% vs 13.2%, P=0.10, OR =0.603, 95% CI 0.33-1.1).

Post-operative tachycardia was a very important complication. In this study, 25 (11.1%) patients in the placebo group and 6.2% (14/227) in the dexmedetomidine group had post-operative tachycardia. Differences, however, were not statistically significant (**Figure 5**, P=0.063, OR=0.528, 0.267-1.045).

Discussion

The present study found that, in elderly patients after total hip or knee replacement surgery, a prophylactic low-dose dexmedetomidine infusion after surgery can significantly decrease

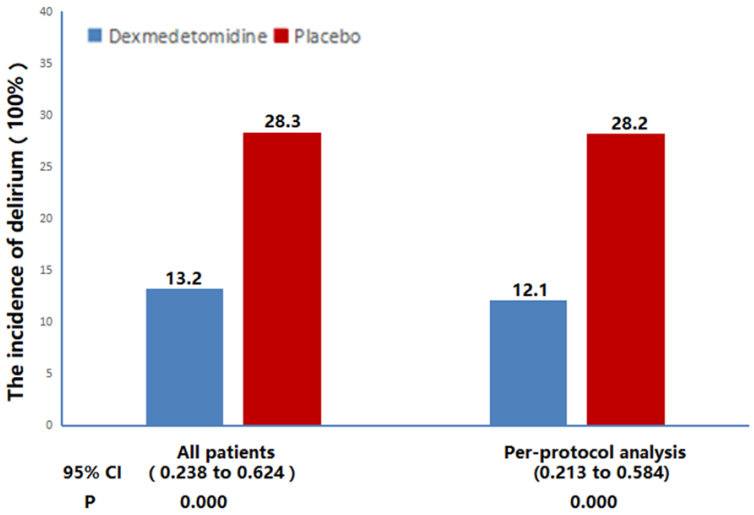

Figure 3. Primary composite endpoint. Incidence of delirium and per-protocol analysis demonstrated a significant reduction in incidence of delirium between the two groups.

incidence of postoperative delirium. Dexmedetomidine supplementation improved analgesia quality and reduced morphine consumption after surgery. It also shortened the length of stays in the hospital and decreased hospitalization expenses, while post-operative complications, like hypertension and tachycardia, were similar.

Postoperative delirium occurred in 28.3% of placebo patients, similar to previous studies [1, 11, 16-18]. Bruce reported by other large studies of hip fracture patients that the frequency of delirium was as high as 51%. Another multicenter double-blind randomized controlled trial also had similar study results, indicating that postoperative delirium was 25.5% with hip fractures [18]. Previous studies have indicated that adults aged 70 and older, with uncontrolled pain, dehydration, those with comorbidities, those using mechanical ventilation, and those taking more than three prescription medications are at greater risk of delirium after hip or knee arthroplasty [19, 20]. Delirium has been associated with increased mortality, morbidity, prolonged hospital stays, worse functional recovery, and decreased long-term cognitive function [1-5]. Importantly, postoperative delirium can increase the risk of a person experiencing poorer cognitive and functional outcomes [21]. Furthermore, postoperative delirium may have significant financial implications for both the patient and the broader health sector, in part due to the extended hospital admissions associated with this diagnosis [21]. Thus, it is very important to control and prevent postoperative delirium.

Postoperative delirium is a very important complication in older patients that can affect surgical success and prognosis. To date, systematic reviews of RCTs have failed to identify a safe and effective pharmacologic strategy to either prevent or treat delirium in critically ill adults [22]. Some very important and high quality RCT studies have also had disappointing results [23-25]. Van den Boogaard [23] reported that both of 1-mg haloperidol and 2-mg haloperidol did not improve survival at 28 days, along with delirium incidence, delirium-free, coma-free days, duration of mechanical ventilation, ICU, and hospital length of stays. Page VJ [24, 25] found that results did not support haloperidol and simvastatin modified duration of delirium in critically ill patients. Finally, no clinical interventional studies evaluating a pharmacologic prevention strategy have considered patient perceptions of the often nightmare-like symptoms associated with delirium that have been described in qualitative studies.

Dexmedetomidine, with its potent and specific affinity of a2-adrenergic receptors agonist, with anxiolytic, sedative, and analgesic properties, has been widely used as an adjuvant during general anesthesia and an anti-delirium agent for sedation in mechanically ventilated patients in the ICU [9, 11, 26, 27]. It has been used by intensivists in general practice for sedation in mechanically ventilated ICU patients at an infusion rate from 0.2 to 1.7 μg/kg per hour with or without a loading dose [9, 11, 27]. Lee [27] also reported a double blind randomized controlled study about dexmedetomidine, indicating that low-doses (1 μg/kg bolus followed by 0.2 to 0.7 μg/kg/h infusion from induction of anesthesia to the end of surgery) decreased the incidence and severity of postoperative delirium, with similar results in a second day for those that received dexmedetomidine (1 μg/kg bolus 15 minutes before the end of surgery). Most previous studies have demonstrated that the effects

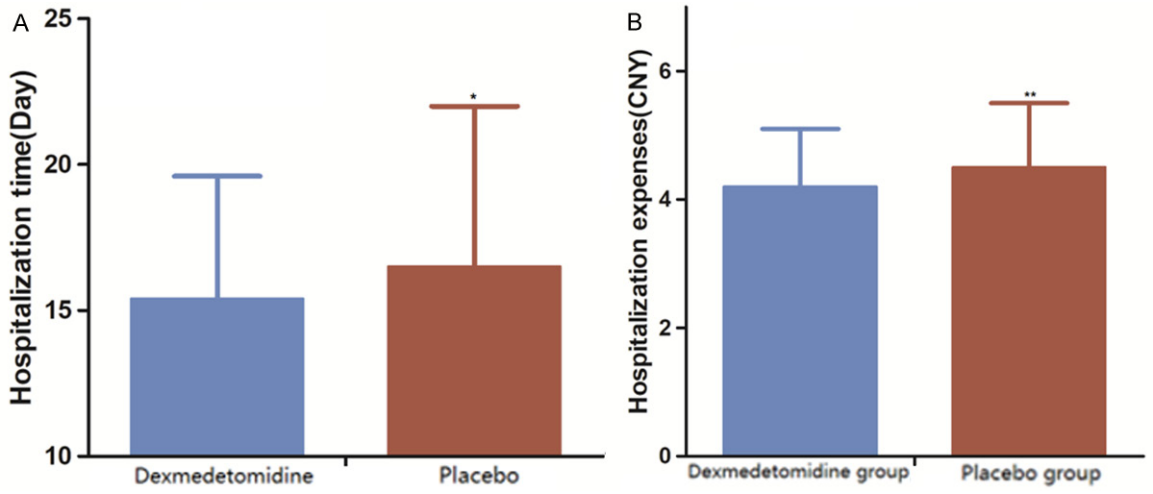

Figure 4. Secondary endpoint. Hospitalization time (A) and hospitalization expenses (B) in the placebo group were significantly increased more than the dexmedetomidine group (*P and **P<0.05).

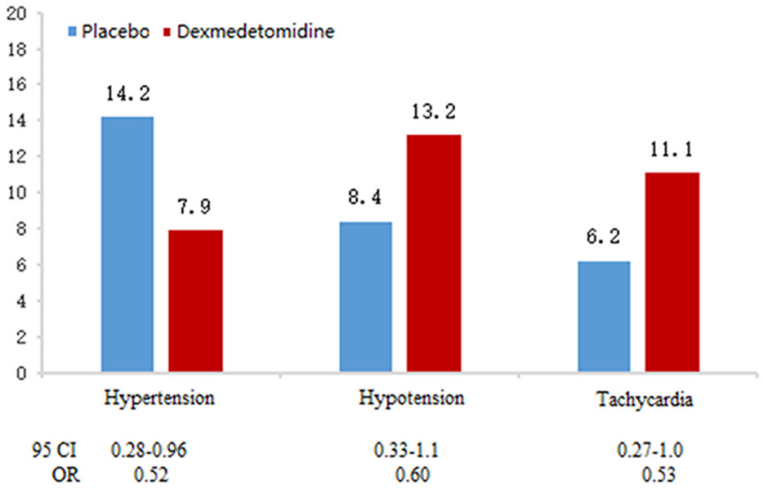

Figure 5. Safety evaluation-postoperative complications. Occurrence of post-operative hypertension was lower in the dexmedetomidine group than in the placebo group. The differences of post-operative tachycardia and hypotension had no statistical significance.

of dexmedetomidine on postoperative delirium were does-dependent, indicating that low-doses can significantly decrease postoperative delirium [11, 26, 27]. This dose of dexmedetomidine has been associated with adverse events, especially for hypotension and bradycardia. This study also evaluated all complications, finding that no patients were removed from the study due to safety issues. This study used 0.1 μg/kg per hour of dexmedetomidine within 3 days after joint replacement surgery, demonstrating a lower severity of postoperative delirium compared with the placebo group. Deiner [28] found that intraoperative dexmedetomidine does not prevent postoperative delirium.

Management of pain and sleep in the elderly is a very important factor in the development of postoperative delirium [11, 29]. Su [11] reported that dexmedetomidine infusion can significantly improve the subjective sleep quality of postoperative ICU patients. Both Su [11] and Liu [29] found that postoperative pain was alleviated appropriately and in a timely manner by used dexmedetomidine infusion.

As for the effects of dexmedetomidine on blood pressure and heart rates, present data demonstrated that the differences of hypotension and tachycardia in the two groups had no statistical significance. Hypertension was significantly decreased in the dexmedetomidine group, however.

The trial recruitment was decelerated after warnings from the Chinese Food and Drug Administration and the Department of Health of Wuxi, warning in October 2015 that the highest approved dose of dexmedetomidine (0.1 μg/kg per hour of dexmedetomidine within 3 days) was associated with an elevated risk of hypotension, tachycardia, and kidney function or myopathy. The everyday clinical data also

was monitored by Hospital Rational and Health Drug Use Review Committee. Safety data were reviewed and it was decided that the study should continue.

The present trial had several strengths. First, the trial included many patients, it was masked, and more than 90% (425/453) of patients were followed up for assessment of clinically relevant outcomes. Second, dexmedetomidine treatment was well-tolerated and no patients developed reversible side effects that required earlier cessation of dexmedetomidine treatment. Third, it used a double-blind, multicenter, randomized, and placebo-controlled design.

Limitations of this study were as follows: ① Collected key baseline and outcome data but did not call patients back for study visits for detailed assessment of quality of life as activities of daily living (ADL). This study was designed to evaluate whether dexmedetomidine improved clinical outcomes and reduced postoperative delirium after joint replacement in elderly patients. ② All participants were screened and enrolled after ICU admission and did not have baseline delirium assessment with cognitive function assessment. ③ This study did not include other operative patients. ④ The duration of infusion of dexmedetomidine was limited to a maximum of 3 days. If patients required postoperative sedation beyond 3 days, then dexmedetomidine was replaced with a midazolam infusion. ⑤ This study used a single dose of dexmedetomidine. The conventional low dose may not work well. ⑥ This study should have checked clinical factors, such as subjective sleep quality, pain, daily prevalence of delirium, and time to extubation.

Conclusion

Results from this trial demonstrate that acute dexmedetomidine therapy reduces postoperative delirium after joint replacement. No evidence was found that low-dose dexmedetomidine increased the prevalence of bradycardia or hypotension, but significantly decreased the prevalence of hypertension. Additionally, it significantly decreased hospitalization expenses and hospitalization time. Whether the favorable effects afforded by this novel application of dexmedetomidine will result in improved long-term outcomes remains unknown. Further investigation of patients undergoing other operations and different doses are necessary to fully understand the potential usefulness of dexmedetomidine in postoperative patients.

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Disclosure of conflict of interest

None.

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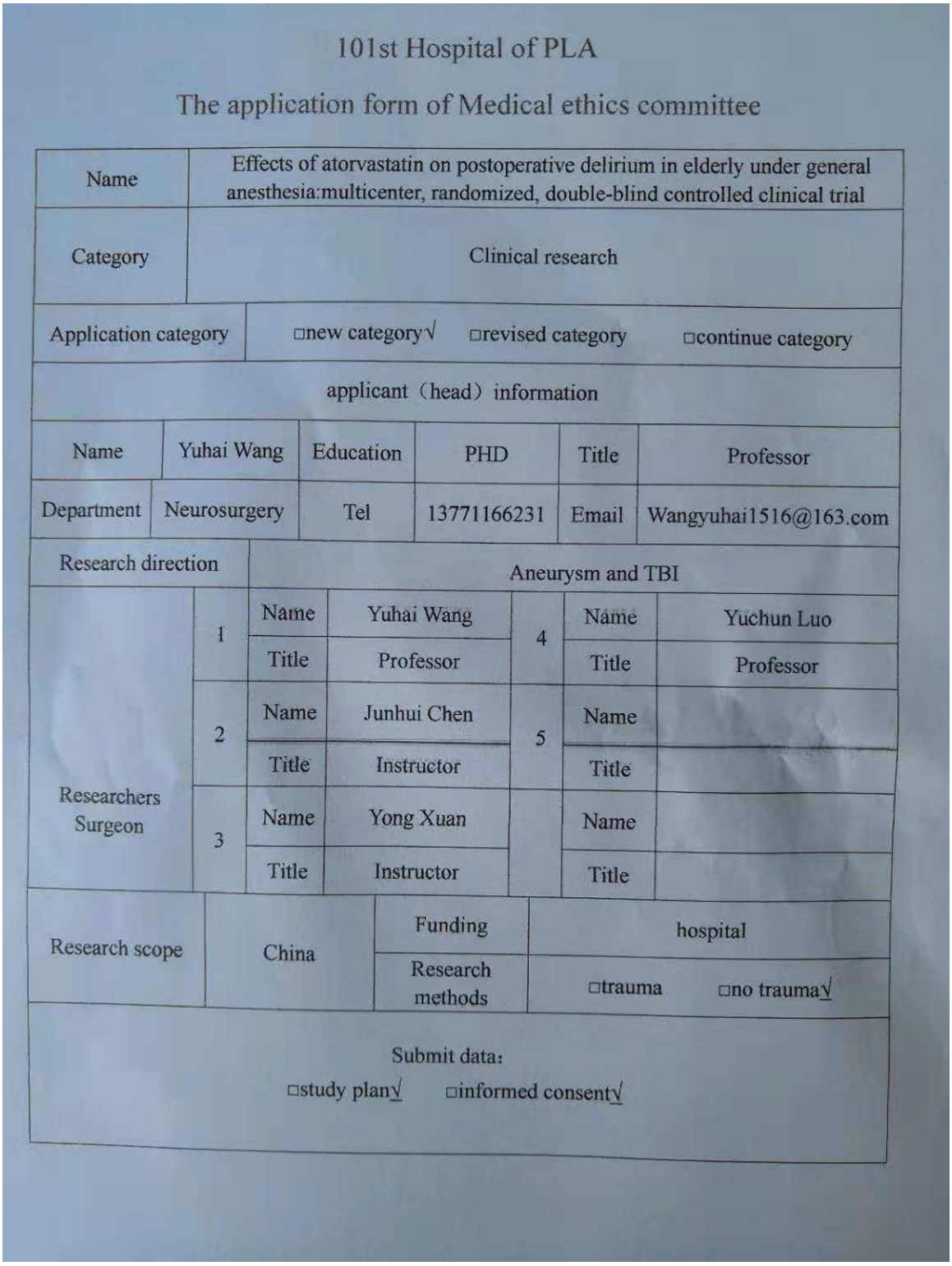
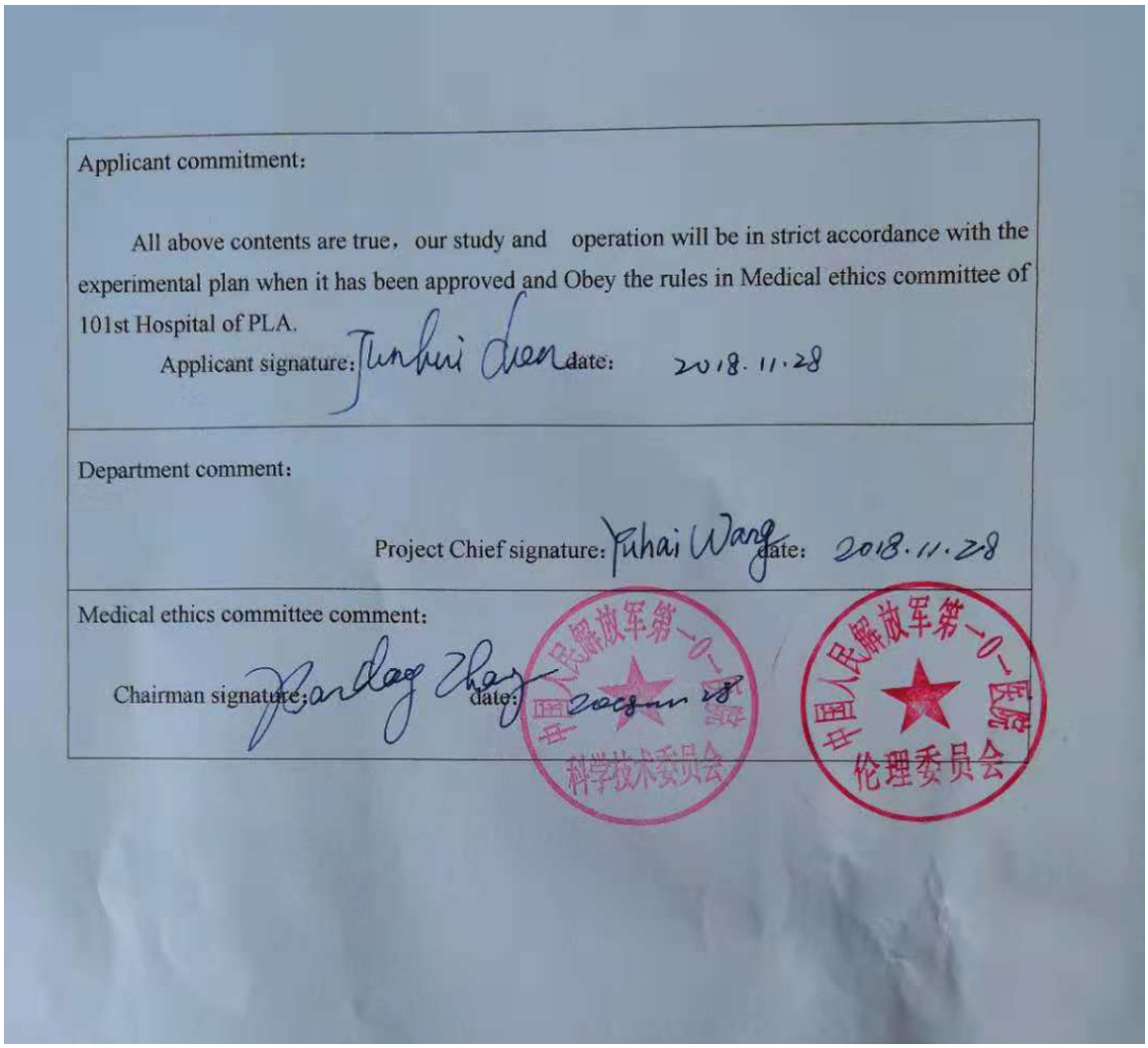


101st Hospital of PLA

The application form of Medical ethics committee

Name	Effects of atorvastatin on postoperative delirium in elderly under general anesthesia:multicenter, randomized, double-blind controlled clinical trial						
Category	Clinical research						
Application category	□new category√ □revised category □continue category						
applicant（head）information							
Name	Yuhai Wang	Education	PHD	Title	Professor		
Department	Neurosurgery	Tel	13771166231	Email	Wangyuhai1516@163.com		
Research direction	Aneurysm and TBI						
Researchers Surgeon	1	Name	Yuhai Wang	4	Name	Yuchun Luo	
		Title	Professor		Title	Professor	
	2	Name	Junhui Chen	5	Name		
		Title	Instructor		Title		
	3	Name	Yong Xuan		Name		
		Title	Instructor		Title		
Research scope	China	Funding	hospital				
		Research methods	□trauma □no trauma√				
Submit data: □study plan√ □informed consent√							



Applicant commitment:

All above contents are true, our study and operation will be in strict accordance with the experimental plan when it has been approved and Obey the rules in Medical ethics committee of 101st Hospital of PLA.

Applicant signature: Junhui Chen date: 2018.11.28

Department comment:

Project Chief signature: Yuhai Wang date: 2018.11.28

Medical ethics committee comment:

Chairman signature: Jiandong Zhang date: 2018.11.28

Appendix. The application form of Medical Ethics from our Anhui Medical University Affiliated Wuxi Clinical College Clinical Research Ethics Committees.