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Original Article

Dexmedetomidine reduces brain neuronal injuries but not clinical neurocognitive function in the elderly, compared to midazolam

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Abstract: Growing evidence has shown that the elderly population is more susceptible to postoperative cognitive dysfunction/decline (POCD). It has been proven that dexmedetomidine can reduce postoperative cognitive function impairment in elderly patients. Whether dexmedetomidine is better than midazolam in reducing incidence of POCD in elderly surgical patients, however, remains unknown. A total of 198 surgery patients (non-cardiac and non-neurosurgery) were enrolled in the current study. A total of 98 patients (DEX group) received a dose of 0.5 ug/kg dexmedetomidine before the induction of general anesthesia. Another 100 patients (MZ group) received midazolam 0.05 mg/kg. Serum samples of S100β protein levels were determined immediately before the application of dexmedetomidine or midazolam and 1 hour after surgery. The Mini Mental State Examination (MMSE) was evaluated at the day before surgery, 5-7 days postoperative, and 3 months postoperative. Results showed that, at 5-7 days after surgery, 52 (26%) patients experienced POCD, with 24 (24.5%) in the DEX group and 28 (28.0%) in the MZ group (24 VS 28, P = 0.575). Three months after surgery, 132 patients accepted the MMSE test, with 16 (12.1%) of them experiencing POCD, including 9 (12.9%) in the DEX group and 7 (11.7%) in the MZ group (9 VS 7, P = 0.783). Increased levels of S100β protein were higher in the MZ group than DEX group (100.68 ± 94.37 pg/mL VS 51.33 ± 88.78 pg/mL, P < 0.001). Logistic regression analysis showed that postoperative pneumonia (incidence of postoperative pneumonia in POCD group VS non-POCD group was 0.12 ± 0.32 VS 0.08 ± 0.28 respectively, P = 0.041), lower preoperative MMSE scores (22.83 ± 3.49 VS 25.55 ± 3.27, P < 0.001), and increased levels of S100β (134.80 ± 81.63 VS 55.40 ± 90.41, P < 0.001) were risk factors of POCD occurring within 5-7 days after surgery. Age was included in the risk factors of POCD occurring within 3 months postoperative (71.56 ± 4.35 VS 69.22 ± 4.29, P = 0.031), except for lower preoperative MMSE scores (24.75 ± 3.53 VS 25.94 ± 2.96, p = 0.001) and increased levels of S100β (92.08 ± 74.12 VS 69.70 ± 95.84, P = 0.002). Present results indicate that dexmedetomidine can reduce neuronal injuries but can't reduce incidence of POCD in the elderly, compared with midazolam. Risk factors for POCD occurring at different postoperative periods are different. Age is a potential risk factor of long-term POCD, but not for early POCD in the elderly.

Keywords: Postoperative cognitive dysfunction (POCD), dexmedetomidine, midazolam, S100β, elderly

Introduction

Clinical evidence has shown higher incidence of postoperative cognitive dysfunction/decline (POCD) in elderly patients having undergone surgery [1]. Incidence of POCD (shown by neurological function tests) at 1 week, 3 months, and 1 year after major non-cardiac surgeries in the elderly were 26% to 58%, 10% to 26%, and 46% to 84%, respectively [2-5]. It is expected that the elderly over 65 years old will account for the highest population experiencing surgery in 2020 [6]. The mechanisms and pathophysiology of POCD are not well known, however [7]. Multiple factors can affect incidence of POCD, such as genetics, aging, education, comorbidities, type of surgery, type of anesthesia, and preoperative cognition. These are the reasons that no specific medicines are available to prevent occurrence of POCD or treat POCD once it develops.

Dexmedetomidine is a highly selective α2-adrenoreceptor agonist with sedative, analgesic, and sympatholytic effects. It is widely used in clinical anesthesia as an adjunct sedative in elderly patients [8]. Adrenergic signaling pathway plays an important role in the formation of cognition. Moreover, α2-adrenoceptors (α2-ARs) regulate the formation of memory, learning, and selective attention by ascending dorsal noradrenergic bundles from the locus ceruleus in the brainstem. It has been confirmed that dexmedetomidine provides neuroprotective effects [9-14] by inducing extracellular signal-regulated kinase (ERK) phosphorylation [15].

S100β protein is one of the calcium binding proteins produced by neural astroglial and Schwann cells [16]. S100β plays critical roles in neuron proliferation and cytoskeletal structure development [17]. Levels of S100β in blood and cerebrospinal fluid are elevated significantly when the brain is damaged [18-20]. Therefore, it has been considered as a marker of neuronal injuries, such as brain traumas, blood-brain barrier disruption, and cerebra ischemia [18, 21-23]. Levels of S100β protein in serum positively correlate with Clinical Dementia Rating Scales Scores and negatively correlate with Mini Mental State Examination (MMSE) scores in Alzheimer's disease (AD) patients [24]. The aim of this study was to clarify whether dexmedetomidine is superior to midazolam in reducing incidence of POCD and neuronal injuries in the elderly after non-cardiac or non-neurosurgery.

Materials and methods

Patients

This study complied with the Helsinki Declaration of 1975 and its subsequent revisions, as well as with Australian National Health and Medical Research Council (NHMRC) guidelines. The study was carried out at the First Affiliated Hospital of Nanchang University (between May 2012 and April 2013) after approval by the Ethics Committee of the hospital. Informed consent was provided by each participant. Inclusion criteria were: Age ≥ 65 years old, American Society of Anesthesiologists (ASA) physical status of I, II or III, operative time of about 2-4 hours, with the ability to complete mini mental state examination (MMSE), preoperative MMSE scores > 15, no significant evidence of serious central nervous, cardiovascular, respiratory, renal or hepatic disease, no usage history of antidepressant, benzodiazepine, alcohol, cigarette misuse, drug dependence, and no contraindications to dexmedetomidine or midazolam. Incidence of POCD in elderly patients was about 40% [25]. The pre-experiment showed efficacy improvement of dexmedetomidine for POCD was about 25% (maximum error was 5% and statistical power was 90%). Therefore, the estimated sample size was 92 cases for each group. The objective of the present study was to compare the treatment effects of dexmedetomidine and midazolam on POCD. Two hundred elderly patients undergoing selective orthopedic surgery, abdominal surgery, and thoracic surgery, with general anesthesia, were enrolled and randomly allocated into the DEX group and MZ group.

Exclusion criteria: Preoperative bradyarrhythmia (heart rate < 50 beats/min), central nervous system or mental disease, use of sedatives or analgesics recently, renal and/or hepatic dysfunction, chronic alcohol or drug abuse, life expectancy of less than three months, massive blood loss (> 1500 mL), MMSE scores lower than 15 before surgery[5], and refusal to participate in the study.

Anesthesia and drug application

Electrocardiogram (ECG), peripheral oxygen saturation (SpO_2), non-invasive arterial pressure (NIBP), end tidal carbon dioxide ($P_{ET}CO_2$), and bispectral index (BIS) were monitored for all patients. Ten minutes before anesthesia induction, 0.5 ug/kg dexmedetomidine was intravenously infused (in 10 minutes) to patients in DEX group, while 0.05 mg/kg midazolam was infused to those in the MZ group. Investigators and patients of this study were all blinded about DEX or MZ infusion. Thereafter, patients in both groups were induced with propofol 1-1.5 mg/kg, fentanyl 3-4 μg/kg, and vecuronium 0.1 mg/kg. General anesthesia depth was maintained at bi-spectral index (BIS) values of 40-60 with propofol (4-12 mg/kg/h) and remifentanil (0.1-0.3 μg/kg/min). Vecuronium (0.03 mg/kg) was injected intermittently when needed. Mechanical ventilation was maintained with a tidal volume of 8-10 mL/kg. Ventilator frequency was adjusted to maintain $P_{ET}CO_2$ at 35-45 mmHg and saturation of pulse

Table 1. Demographics and characteristics of patients in the DEX group and MZ group

Variables	DEX group (n = 98)	MZ group (n = 100)	*t value*	*p value*
Gender (M/F)	66/32	66/34	Pearson = 0.40	0.881
Age (years)	70.47 ± 4.95	69.36 ± 4.51	0.015	0.884
Weight (kg)	56.42 ± 9.74	57.07 ± 9.79	0.128	0.639
Education (y)	3.85 ± 3.73	4.36 ± 4.39	0.013	0.879
ASA (I/II/III)	0/73/25	3/76/21	Pearson = 3.388	0.184
Type of surgery (orthopedic/abdominal/thoracic)	7/84/7	10/74/16	Pearson = 4.664	0.097
Preoperative MMSE score	24.87 ± 3.91	25.03 ± 3.30	0.317	0.752
levels of S100β preoperative	457.68 ± 131.24	442.48 ± 135.74	0.801	0.424

oximetry (SPO_2) at 98-100%. The infusion of propofol and remifentanil were terminated 5 minutes before the end of the surgery. After surgery, all patients accepted similar patient-controlled intravenous analgesia to alleviate acute pain.

Data collection

Age, gender, years of education, surgery history, type of present surgery, comorbidities (such as diabetes mellitus, hypertension, and cardiovascular disease) [26], postoperative complications (such as pneumonia, postoperative sepsis, and postoperative hemorrhage shock) were collected. Diagnostic criteria for postoperative pneumonia included coughing, increased white blood cells, and fever [27]. Intraoperative hypotension [28] and the use of atropine [29] were recorded. These variables were considered as risk factors of POCD. MMSE scores were evaluated at the day before surgery, 5-7 days, and 3 months after surgery by well-trained anesthesia nurses.

Enzyme linked immunosorbent assay (ELISA)

Intravenous blood was sampled immediately before the application of dexmedetomidine or midazolam and 1 hour after surgery. Serum was collected by centrifuging the blood samples at 2,000 rpm for ten minutes, storing at -80°C until use. S100β protein concentrations in the serum were measured using the ELISA kit, according to manufacturer instructions.

Statistical analysis

Age, weight, education, MMSE scores preoperative, levels of S100β preoperative, and increased levels of S100β (postoperative levels subtracted that of preoperative) between the DEX group and MZ group were analyzed with Student's *t* test. Categorical variables (gender, ASA, type of surgery) between the DEX group and MZ group were evaluated using Pearson's Chi-squared analyses. Risk factors for POCD were analyzed with logistic regression analysis. POCD occurring within 5-7 days or 3 months after surgery was considered as a dependent variable, while age, gender, education levels, type of surgery, hypotension, postoperative pneumonia, second surgery, inhalational anesthetics, diabetes mellitus, perioperative hypertension, preoperative MMSE scores, increased levels of S100β, and the use of dexmedetomidine, midazolam, and atropine were considered as covariates in logistic regression analyses. In a forward selection procedure in logistic regression models, all variables with *p*-values above 0.05 were removed. All analyses were performed using SPSS 18.0 software (SPSS Inc, Chicago, IL). Moreover, p values < 0.05 indicate statistical significance.

Results

Characteristics of patients

Of the 200 elderly patients, 2 patients in the DEX group were excluded because of intraoperative massive blood loss (> 1500 mL). There were 198 patients involved the study, with 98 in the DEX group and 100 in the MZ group. There were no significant differences in patient characteristics between the two groups (**Table 1**).

Incidence of POCD

MMSE scores were evaluated by well-trained anesthesia nurses for each subject at the day before surgery, 5-7 days after surgery (face to face in ward), and 3 months postoperative

Table 2. Comparison of POCD incidence at 5-7 days and 3 months after surgery

Time	DEX group (n = 98)	MZ group (n = 100)	*p* value
5-7 days postoperative	24/98 (24.5%)	28/100 (28.0%)	0.575
3 months postoperative	9/70 (12.9%)	7/62 (11.3%)	0.783

Note: POCD was defined if the MMSE score decreased 3 or more scores than preoperative.

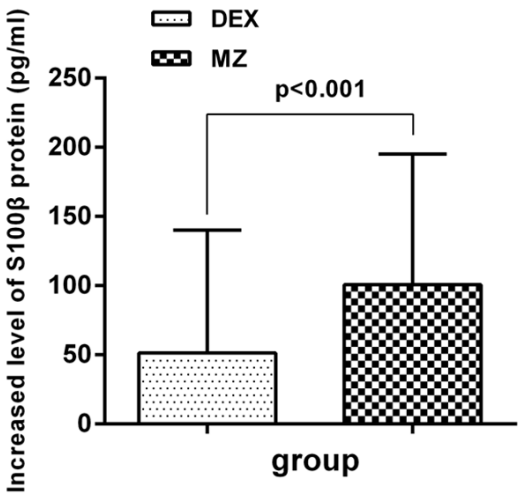

Figure 1. Serum levels were detected immediately before the application of dexmedetomidine or midazolam and 1 hour after surgery. Increased levels of S100β were calculated by subtracting the preoperative levels from those of postoperative. Increased levels of S100β in the DEX group were significant lower than the MZ group (51.33 ± 88.78 pg/mL VS 100.68 ± 94.37 pg/mL, P < 0.001).

(telephone follow-up). POCD was defined as MMSE scores declined by one standard deviation (SD) or more than preoperative MMSE scores [5]. In the present study, one standard deviation of the MMSE preoperative was nearly 3 scores. Therefore, POCD was defined if the MMSE scores decreased 3 scores or more than preoperative. There were 52 (26.3%) patients experiencing POCD at 5-7 days after surgery, 24 (24.5%) of them in the DEX group and 28 (28.0%) in the MZ group (**Table 2**). There were no differences in incidence of POCD between the two groups (*P* = 0.345). There were 132 (70 in DEX group, 62 in MZ group) patients that finished the MMSE test at 3 months after surgery. The other 68 patients discontinued the study due to death, severe illness, or refusal to continue the study. Sixteen (12.1%) experienced POCD at 3 months after surgery, with 9 (12.9%) in the DEX group and 7 (11.3%) in the MZ group (9 VS 7, P = 0.498).

Serum S100β

Serum levels were detected immediately before the application of dexmedetomidine or midazolam 1 hour after surgery. Increased levels of serum S100β protein in the DEX group were significantly lower than the MZ group (P < 0.001) (**Figure 1**), indicating that dexmedetomidine can reduced brain neuronal injuries, compared to midazolam.

Risk factors for POCD

Risk factors for POCD were analyzed by logistic regression analysis. POCD occurring within 5-7 days or 3 months after surgery was considered as a dependent variable, while 16 potential risk factors (see Statistical Analysis section) were considered as covariates. Results showed that postoperative pneumonia (P = 0.041), lower preoperative MMSE scores (P < 0.001), and increased levels of S100β (P < 0.001) were risk factors of POCD occurring within 5-7 days after surgery (**Table 3**). In addition to lower preoperative MMSE scores (P = 0.001) and increased levels of S100β (P = 0.002), age was also included in the risk factors of POCD occurring within 3 months after surgery (P = 0.031) (**Table 4**).

Discussion

The present study showed that postoperative pneumonia, lower preoperative MMSE scores, and increased levels of S100β were risk factors for POCD occurring within 5-7 days after surgery. In addition to lower preoperative MMSE scores and increased levels of S100β, age was also included in the risk factors of POCD occurring within 3 months after surgery. Compared to midazolam, dexmedetomidine can reduce neuronal injuries but can't reduce incidence of POCD in the elderly undergoing non-cardiac or non-neurosurgery.

Incidence of POCD at 5-7 days and 3 months after surgery was 26.3% and 12.1%, respectively, in the present study. This was in accord with that of the International Study of Postoperative Cognitive Dysfunction (ISPOCD) [2], which showed that incidence of POCD at 7 days and 3 months after non-cardiac surgery was 26% and 10%, respectively.

Table 3. Risk factors of POCD occurring at 5-7 days postoperative

Variable	B	S.E.	*p value*	*Odds ratio*	*95% CI. For OR*	
					Lower	*Upper*
Increased levels of S100β	0.011	0.002	< 0.001	1.011	1.006	1.015
Preoperative MMSE score	-0.086	0.012	< 0.001	0.918	0.896	0.940
Postoperative Pneumonia	1.136	0.557	0.041	3.116	1.047	9.274

Note: Increased levels of S100β were calculated by subtracting the preoperative levels from postoperative levels.

Table 4. Logistic regression analyses model predicting risk factors of POCD at 3 months postoperative

Variable	B	S.E.	*p* value	Odds ratio	95% CI. For OR	
					Lower	Upper
Increased levels of S100β	0.008	0.002	0.002	1.008	1.003	1.013
Preoperative MMSE score	-0.194	0.060	0.001	0.824	0.732	0.927
Age	0.047	0.022	0.031	1.048	1.004	1.094

POCD was defined with memory, executive function, attention, learning, language, and visual spatial skill and mathematics impairment. MMSE is the most commonly used composite measure to identify POCD [7]. Total scores of MMSE are 30, including 10 scores of disorientation, 3 scores of memory, 3 scores of learning, 5 scores of mathematics or attention, 6 scores of language, 2 scores of executive function, and 1 score of visual spatial skill. To evaluate incidence of POCD more exactly, this study excluded the MMSE test confounding factors through the same test and a similar test environment. MMSE scores for all patients were evaluated by the same anesthesia nurses (blinded to the use of dexmedetomidine and midazolam) at the day before surgery, 5-7 days after surgery, and 3 months after surgery.

Previous studies have suggested that dexmedetomidine may provide neuroprotective effects for traumatic, ischemic, or sepsis brains. The current study showed no significant differences in incidence of POCD at 5-7 days (24 VS 28, P = 0.575) or 3 months after surgery (9 VS 7, P = 0.783) between the DEX group and MZ group. Results indicate that dexmedetomidine cannot reduce incidence of POCD in the elderly, compared to midazolam. Dosage of dexmedetomidine, surgery type, and diagnosis of POCD may be some of the reasons why there were no significant effects on reducing incidence of POCD [30, 31].

To identify whether this dosage of dexmedetomidine had protective effects on neurons, serum levels of S100β protein were detected before and 1 hour after surgery. Results showed that serum levels of S100β increased significantly after surgery in both groups. However, increased levels of S100β in the DEX group were much lower than the MZ group, suggesting that dexmedetomidine can reduce neuronal injuries in elderly patients undergoing elective non-cardiac surgery, compared to midazolam. Sato et al. [11] demonstrated that dexmedetomidine can attenuate cerebral ischemic rat neuronal injuries in the hippocampal CA1 region. Previous clinical evidence has shown that dexmedetomidine could provide more days without brain dysfunction and mechanical ventilation, with less mortality in septic patients [10].

Present results demonstrate that postoperative pneumonia, lower preoperative MMSE scores, and increased levels of S100β were risk factors of POCD occurring within 5-7 days after non-cardiac or non-neurosurgery in older patients. Mary Beth Harrington et al. [32] showed that patients with preoperative cognitive deficits were less likely to rehabilitate to baseline after cardiac surgery. Patients with mild cognitive impairment had a greater decline in performance in the Digit Span Forward test after surgery [33]. Except for lower preoperative MMSE scores and increased levels of S100β, age was also involved in the risk factors of POCD occurring within 3 months after surgery. Present results indicate that potential risk factors for POCD occurring at different postoperative stages were different. Postoperative pneumonia complications potentiate occurrence of POCD in early postoperative stages, but not for those occurring at 3 months after surgery. In contrast, age is one of the risk factors of long-term POCD after surgery in the elderly, but not a risk factor of POCD occurring

at early postoperative stage. Results from Carmen et al. also showed that age has no relationship to POCD in early postoperative stages [34]. Another possible reason may be associated with the fact that cognitive function declines with aging, especially in the elderly [35]. Postoperative pneumonia is an acute pulmonary complication after surgery, which cause systematic inflammation. Previous studies have confirmed that inflammation plays critical roles in the pathogenesis of postoperative delirium in intensive care units [36]. Early POCD may be much more correlative with inflammatory mediators [37].

It has been confirmed that serum S100β protein levels are elevated when the brain is damaged, suggesting that S100β could be a biomarker of neuronal injuries [20]. Increased levels of S100β in the DEX group were much lower than the MZ group, but incidence of POCD was similar in the two groups. Logistic regression analysis showed that increased levels of S100β were one of the risk factors of POCD. These results suggest that S100β protein may be more sensitive than the MMSE score system in detecting neuronal injuries.

This study had several limitations, however. This study had no saline control group. Therefore, this study concluded that the dexmedetomidine treated-group had lower increased S100β levels than the midazolam group. However, it was difficult to clarify whether dexmedetomidine can prevent neuronal injuries induced by surgery or only reduce neuronal injuries, to some degree. This study also could not conclude the exact effects of midazolam on neuronal injuries. Does it protect or deteriorate the injury? There has been no evidence that midazolam could increase S100β levels in serum, thus far. In addition, this study evaluated cognition only with MMSE. This may have resulted in lower incidence of POCD. Multiple cognition assessment systems should be used to evaluate cognition in future studies.

In conclusion, present results indicate that dexmedetomidine could reduce neuronal injuries but not incidence of POCD induced by surgery, compared to midazolam, in elderly patients undergoing non-cardiac or non-neurosurgery. The risk factors profile for POCD occurring at different postoperative periods was different. Age is a potential risk factor of long term POCD, but not for early POCD.

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Disclosure of conflict of interest

None.

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