Effects of propofol, dexmedetomidine, and midazolam on postoperative cognitive dysfunction in elderly patients: a randomized controlled preliminary trial

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Abstract

Background: Postoperative cognitive dysfunction (POCD) is a serious complication after surgery, especially in elderly patients. The anesthesia technique is a potentially modifiable risk factor for POCD. This study assessed the effects of dexmedetomidine, propofol or midazolam sedation on POCD in elderly patients who underwent hip or knee replacement under spinal anesthesia.

Methods: The present study was a prospective randomized controlled preliminary trial. From July 2013 and December 2014, a total of 164 patients aged 65 years or older who underwent hip or knee arthroplasty at China-Japan Friendship Hospital and 41 non-surgical controls were included in this study. Patients were randomized in a 1:1:1 ratio to 3 sedative groups. All the patients received combined spinal-epidural anesthesia (CSEA) with midazolam, dexmedetomidine or propofol sedation. The sedative dose was adjusted to achieve light sedation (bispectral index[BIS] score between 70 and 85). All study participants and controls completed a battery of 5 neuropsychological tests before and 7 days after surgery. One year postoperatively, the patients and controls were interviewed over the telephone using the Montreal cognitive assessment 5-minute protocol.

Results: In all, 60 of 164 patients (36.6%) were diagnosed with POCD 7 days postoperatively, POCD incidence in propofol group was significantly lower than that in dexmedetomidine and midazolam groups (18.2% *vs.* 40.0%, 51.9%, $\chi^2=6.342$ and 13.603, $P=0.012$ and <0.001). When the patients were re-tested 1 year postoperatively, the incidence of POCD was not significantly different among the 3 groups (14.0%, 10.6% *vs.* 14.9%, $\chi^2=0.016$ and 0.382, $P=0.899$ and 0.536).

Conclusion: Among dexmedetomidine, propofol and midazolam sedation in elderly patients, propofol sedation shows a significant advantage in term of short-term POCD incidence.

Keywords: Cognitive dysfunction; Neuropsychological tests; Postoperative period; Sedatives

Introduction

Postoperative cognitive dysfunction (POCD) is a subtle disorder of thought processes, which might influence isolated domains of cognition, such as verbal memory, visual memory, language comprehension, visuospatial abstraction, attention, or concentration.[1,2] POCD severely interferes with the compliance of postoperative treatment and impairs prognosis and life quality. Due to differences in the definition of POCD, the composition of the test battery, and the time of postoperative assessment, the incidence of POCD reported in different studies varies substantially. The prevalence of POCD ranges from 16% to 62% in patients undergoing hip fracture repair.[3-5] Older patients, in particular, are vulnerable to memory disturbances and other types of cognitive impairment after surgical operations.[6]

The anesthesia technique is a potentially modifiable risk factor for POCD.[7] Compared with general anesthesia, regional anesthesia provides benefits in terms of protecting cognitive function[8] and potentially decreasing mortality and the incidence of POCD early after surgery.[9] Studies have demonstrated that epidural anesthesia decreases the incidence of POCD in elderly patients. Mechanistically, the levels of amyloid-β(Aβ), which induces the early apoptosis

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of neurons,[10] and Tau protein, a biomarker of neuron degeneration,[11,12] were reduced by epidural anesthesia compared with general anesthesia. It has also been shown that limiting the depth of sedation during spinal anesthesia is a simple, safe, and cost-effective intervention for preventing postoperative delirium in elderly patients.[13]

Propofol, midazolam, and dexmedetomidine are widely used sedatives in clinical practice. Midazolam is a sedative commonly used in regional anesthesia, although some studies have noted that it can cause delirium and POCD, especially in elderly patients.[14,15] Propofol is a GABAergic agent. It has been shown that in elderly patients undergoing hip fracture repair under spinal anesthesia with propofol sedation, the prevalence of delirium can be decreased by 50% with light sedation compared with deep sedation.[15] Dexmedetomidine is an alpha-2 adrenoreceptor agonist with a unique mechanism of action. It has been reported that dexmedetomidine can not only provide sedation and anxiolysis but also promote a more physiological sleep pattern without significant respiratory depression. Riker *et al*[16] demonstrated that dexmedetomidine-treated patients in intensive care units experience less delirium than midazolam-treated patients. Djaiani *et al*[17] reported that compared with propofol, dexmedetomidine sedation not only reduced the incidence but also the delayed onset and the shortened duration of postoperative delirium in elderly patients after cardiac surgery. However, there have been no studies focusing on the effect of different sedatives on POCD in elderly patients receiving regional anesthesia.

The primary aim of this study was to evaluate the short-term (1 week postoperatively) and long-term (1 year postoperatively) incidence of POCD after elective joint replacement surgery in patients aged ≥65 years. Elective joint replacement surgery in a standardized perioperative approach was used as a model for major elective non-cardiac surgery in general, since this would enable us to test a series of relatively uniform patients undergoing a standardized surgical procedure receiving similar perioperative care. All patients included in the study received standardized CSEA with light sedation. We evaluated the incidence of POCD in patients with 3 different sedatives.

Methods

Ethical approval

The present study was a prospective randomized controlled preliminary trial. This study was conducted in accordance with the *Declaration of Helsinki* approved by the Ethics Committee of China-Japan Friendship Hospital, Beijing (No.2013-32-k23). Informed written consent was obtained from all patients.

Study design and population

The primary goal of this study was to evaluate the short-term (1 week postoperatively) and long-term (1 year postoperatively) incidence of POCD after elective joint replacement surgery in patients aged ≥65 years. Patients were enrolled in the study between July 2013 and December 2014. Eligible patients were 65 years or older and scheduled to undergo elective unilateral total hip replacement surgery or total knee replacement surgery at China-Japan Friendship Hospital. Participants for the control group were recruited from the community as part of the study. The control subjects were aged 65 years or older and had no surgery planned for the next 12 months. Subjects were excluded from the experimental and control groups if they had contraindications to spinal anesthesia (*eg*, aortic stenosis, coagulopathy, concurrent usage of anticoagulants, spinal cord disease, refusal of spinal anesthesia); severe hepatic and renal insufficiency; stroke or transient ischemic attack in 1 month; an ASA grade higher than III; or anticipated difficulty with neuropsychological assessment, such as receiving less than 9 years of education or having an existing mental disorder.

The sample size was calculated to obtain a power of 0.80 at a significance level of 0.05. We sought to obtain sufficient data on early POCD (at 1–2 weeks) to discern a reduction from the previously reported 45% POCD incidence among the elderly undergoing elective joint replacement surgery to an anticipated level of about 20% which required an evaluation of 42 patients at least in each group. The formula is $n=\left(\frac{Z_{\alpha/2}+Z_{\beta}}{\delta}\right)^2\pi(1-\pi)$, $\alpha=0.05$, $\beta=0.1$, $\delta=0.25$, $\pi=0.45$, $n=42$.

Patients were randomized to receive one of the 3 anesthetics using a random number table at a ratio of 1:1:1. The first patient we selected corresponds to the first number on the random number table, and so on. Then, the number on the random number table divided by 3. If the remaining number is 1 that patient was included in dexmedetomidine group, 2 in propofol group and 0 in midazolam group. An independent staff completed the entire randomization process.

Anesthetic procedure

Patients were not premedicated. Upon admission to the operating room, routine monitoring (non-invasive blood pressure, electrocardiogram, pulse oximetry) was set up. An intravenous cannula was inserted in a forearm vein. A bispectral electrode was positioned on the patient's forehead and connected to a BIS monitor (Aspect Medical Systems, Norwood, MA, USA).

Patients were given combined spinal-epidural anesthesia (CSEA) with light sedation using one of the following sedatives selected randomly: midazolam, propofol or dexmedetomidine. CSEA was established at the L2–3 or L3–4 interspaces with the patient in a lateral position using a needle-through-needle technique. In brief, a 16-gauge epidural Tuohy needle was inserted into the epidural space using the method of loss of resistance to saline. Then, a 26-gauge spinal needle (pencil point tip) was inserted into the intrathecal space passing through the Tuohy needle. After ascertaining the emergence of cerebrospinal fluid, 2 ml of the 0.75% bupivacaine (2 ml of 0.75% bupivacaine diluted by 10% glucose solution to 3 ml) was injected into the intrathecal space within 15 seconds. Finally, the spinal

needle was withdrawn, and an epidural catheter was threaded approximately 3 cm cephalad into the epidural space. The epidural catheter was gently aspirated and checked for the presence of blood or cerebrospinal fluid. Before surgical positioning, patients were maintained in the lateral position for at least 5 minutes after subarachnoid injection to intensify the block at the surgical site.

Patients were randomly assigned to the dexmedetomidine, propofol, or midazolam group. The intravenous infusion rates of dexmedetomidine and propofol, and intravenous bolus injection dosage of midazolam were adjusted to achieve light sedation (BIS score between 70 and 85) during the surgical procedure.

Any intraoperative systolic blood pressure decrease greater than 30% from the preoperative value and/or a systolic blood pressure less than 90 mm Hg (1 mmHg = 0.133 kPa) was defined as hypotension and treated. The initial treatment regimen for hypotension included a fluid bolus followed by phenylephrine via either bolus or infusion. The second-line treatment was ephedrine, depending on the hemodynamic status of the patient. The hypotension duration and the vasoactive drug dosage were recorded.

After surgery, the patients were transferred to the post-anesthesia care unit (PACU) with standard monitoring. When the patients' vital signs were stable and comfortable, they were transferred to the ward for further management.

Patient-controlled epidural analgesia (PCEA) was provided postoperatively for 48 hours. The postoperative analgesia regimen was as follows: 0.2% ropivacaine, 200 mL; background, 4 mL/h; bolus dose, 2 mL; interval, 30 minutes, adjusted individually. Monitoring included continuous pulse oximetry for 24h postoperatively, hourly respiratory rate and sedation level, and 4-hourly blood pressure, pulse rate, numerical rating scale (NRS) pain score, and analgesic-related side effects, including nausea and vomiting. During the postoperative visits, patients were asked to provide detailed information about postoperative analgesia and report any side effects, including nausea, vomiting, dizziness, pruritus, and lower limb weakness (for epidural infusion). In addition, the nursing staff specifically asked about these side effects, while charting the pain scores every 4 hours. Patients were advised to report any other effects that they felt might be related to their treatment.

Neuropsychological testing and the definition of POCD

Neuropsychological tests were administered by research personnel who were trained under the supervision of a neuropsychologist. The majority of the testing was conducted by the same core group of research staff.

The neuropsychological test battery consisted of 5 different tests focusing on different cognitive domains susceptible to dysfunction after surgery:

- Montreal cognitive assessment (MoCA)
- Stroop color-word test (SCWT)
- Digit span test
- Digit symbol test
- Associative learning and memory test

In the MoCA test, the score and the time required for the patient to complete the test were recorded. To evaluate the alterations in cognitive function before and after the operation, we calculated the changes in the scores and test duration. The variation between the initial test and the repeat test (repeat test minus initial test) is the Δ value.

The SCWT assesses the executive functions of inhibition, selective attention, mental speed, and interference susceptibility. Participants were first shown a page with color words printed in black ink and asked to read the word (Card A). Then, participants were shown a page with color dots and asked to name the colors (Card B). Lastly, participants were shown a page with color words printed in non-matching ink (ie, the word blue is printed in red) and asked to name the ink color (Card C). The differences in the test time, and the correction time between the initial and repeated tests indicate the executive component of response inhibition.

In the digital symbol test, the number of correct symbols within the allowed time (90 second) is measured. In the digital span test, the participants try to remember a sequence of numbers and repeat as many as possible forward and backward. The maximum number of digits memorized is recorded.

The patients completed these tests on the day before and 7 days after the operation. To further study the effect of the sedatives on POCD over a relatively long postoperative period, patients were interviewed over the telephone using the 5-minute MoCA protocol 1 year postoperatively.[18] Subjects in the control group also completed the neuropsychological test battery twice with a 7-day interval, as well as the MoCA 5-minute protocol 1 year later.

The diagnosis of POCD was verified by psychometry testing performed pre- and postoperatively to assess cognitive performance. Test scores were analyzed to identify POCD using the reliable change index (RCI). The RCI was calculated following the procedure outlined by Rasmussen *et al*[19] RCIs were determined by subtracting the preoperative score (χ_1) from the postoperative score (χ_2), giving Δ_χ for each individual participant for a given task. The mean expected change for the controls, $\Delta_{\chi c}$, calculated in the same way, was then subtracted from this value, removing any practical effect. This score was then divided by the standard deviation for the change in test results of the control group, SD ($\Delta_{\chi c}$), controlling for the expected variability. These scores were then used to create a combined test score ($Z_{combined}$) using the sum of z scores for each test ($\sum Z_{a,b,c,d,\ldots}$) divided by the standard deviation of this summation in the control group (SD [$\sum Z_{control}$]). POCD was defined in an individual when their RCI score was less than −1.96 on ≥2 tests and/or their combined *z* score was less than −1.96. This classifies POCD based on the substantial failure of more than 2 tests

or a more pervasive subtle decline across the neuropsychological test battery.

Statistical analysis

Group comparisons were made using unpaired *t* tests for continuous variables, or Kruskal-Wallis test for ranked data, and the χ^2or Fisher exact test for dichotomous variables. Tests were performed using SAS 9.2 (SAS Institute Inc, Cary, NC, USA). A value of $P<0.05$ was taken to indicate statistical significance.

Results

From July 2013 to December 2014, 164 patients and 41 control subjects were recruited. The age of the patients in the experimental groups was 68.2±6.7 years, which was not significantly different from that of the control subjects (67.0±6.0 years) [Table 1]. In addition, there were no significant differences in other demographics or comorbidities between the patients and control subjects. The 164 patients were randomly assigned into 3 groups, as follows: 55 patients were allotted to the dexmedetomidine sedation group, 55 patients were assigned to the propofol sedation group, and 54 patients were assigned to the midazolam sedation group [Figure 1]. All experimental groups were similar with respect to demographic data and pre- and intraoperative medications [Table 2]. There were no significant differences among the groups regarding postoperative analgesia, including the dose of ropivacaine, at rest NRS score, active NRS score, and number of bolus doses, on both postoperative days POD 1 and POD 2 ($P>0.05$).

Overall, of the 164 patients enrolled, 60 patients (36.6%) were diagnosed with POCD 7 days postoperatively. POCD incidence in propofol group was significantly lower than that in dexmedetomidine and midazolam groups (18.2% *vs.* 40.0%, 51.9%, $\chi^2=6.342$ and 13.603, $P=0.012$ and <0.001; Table 3).

As many as 12 patients in the dexmedetomidine group, 8 patients in the propofol group and 7 patients in the midazolam group lost to follow-up 1 year after the operation. As much as 13.1% of the patients had POCD 1 year after the operation. The incidence of POCD in the dexmedetomidine sedation group and propofol group was not significantly different from that of midazolam group (14.0%, 10.6% *vs.* 14.9%, $\chi^2=0.016$ and 0.382, $P=0.899$ and 0.536; Table 3).

As shown in Table 4, the Δ value of the overall MoCA score between the day before (initial test) and 7 days after the operation (repeated test) of patients who received midazolam sedation was significantly lower than that of patients who received propofol or dexmedetomidine (−1 [−2 – 1] *vs.* −0[0–3], 1[−1–2], $H=8.344$, $P=0.015$). While the Δ value of the clock-drawing score (subtest of MoCA) of patients who received propofol sedation was significantly lower than that of patients who received dexmedetomidine or midazolam (0 *vs.* 0[0–0.5], 0[−1–0], $H=10.602$, $P=0.005$) Moreover, the Δ value of the overall MoCA and clock-drawing scores in the dexmedetomidine group were markedly higher than those in the propofol and midazolam groups.

In the SCWT, the patients in the midazolam group had fewer corrections on the Card C test than those in the dexmedetomidine and propofol groups (−1[−3– 1] *vs.* 1 [−1–2],−1[−1–1], $H=9.432$, $P=0.009$; Table 5).

In the digital symbol test, we found no significant difference in the number of correct symbols among the patients in the 3 experimental groups [Table 6]. There were no significant differences among the 3 groups in the digital span test and associative learning and memory test results.

Discussion

In this present study, we evaluated the short- and long-term outcomes of POCD in elderly patients undergoing elective joint replacement surgery under spinal anesthesia with light sedation. Among 164 elderly patients, a total of 60 patients (36.6%) were found to have POCD on POD 7. The incidence of POCD was 18.2%, 40.0%, and 51.9% in the propofol, dexmedetomidine, and midazolam groups, respectively. In addition, the difference of POCD incidence among the 3 groups was statistically significant. These results suggest that propofol has the least impact on cognitive function 1 week after the operation, while midazolam tended to impair cognitive function in our patients.

Table 1: Demographics and clinical characteristics of patients in the control group and experimental group.

Parameters	Control group ($n=41$)	Experimental group ($n=164$)	Statistics	*P*
Age (years)	67.0±6.0	68.2±6.7	−1.046*	0.296
Gender (M/F)	18/23	54/110	1.736†	0.080
Height (cm)	163.2±6.8	160.1±7.8	2.332*	0.021
Weight (kg)	63.1±11.9	66.5±10.2	−1.845*	0.067
Education (years)	10.4±2.6	10.8±3.2	0.741*	0.459
Hypertension	10 (24.4)	38 (23.2)	0.027†	0.870
DM	8 (19.5)	31 (18.9)	0.008†	0.929
Cerebrovascular disease history	3 (7.3)	14 (8.5)	0.064†	0.800

* *t* value. † χ^2 value. Data were presented as mean±standard deviation or *n* (%). DM: Diabetes mellitus; F: Female; M: Male.

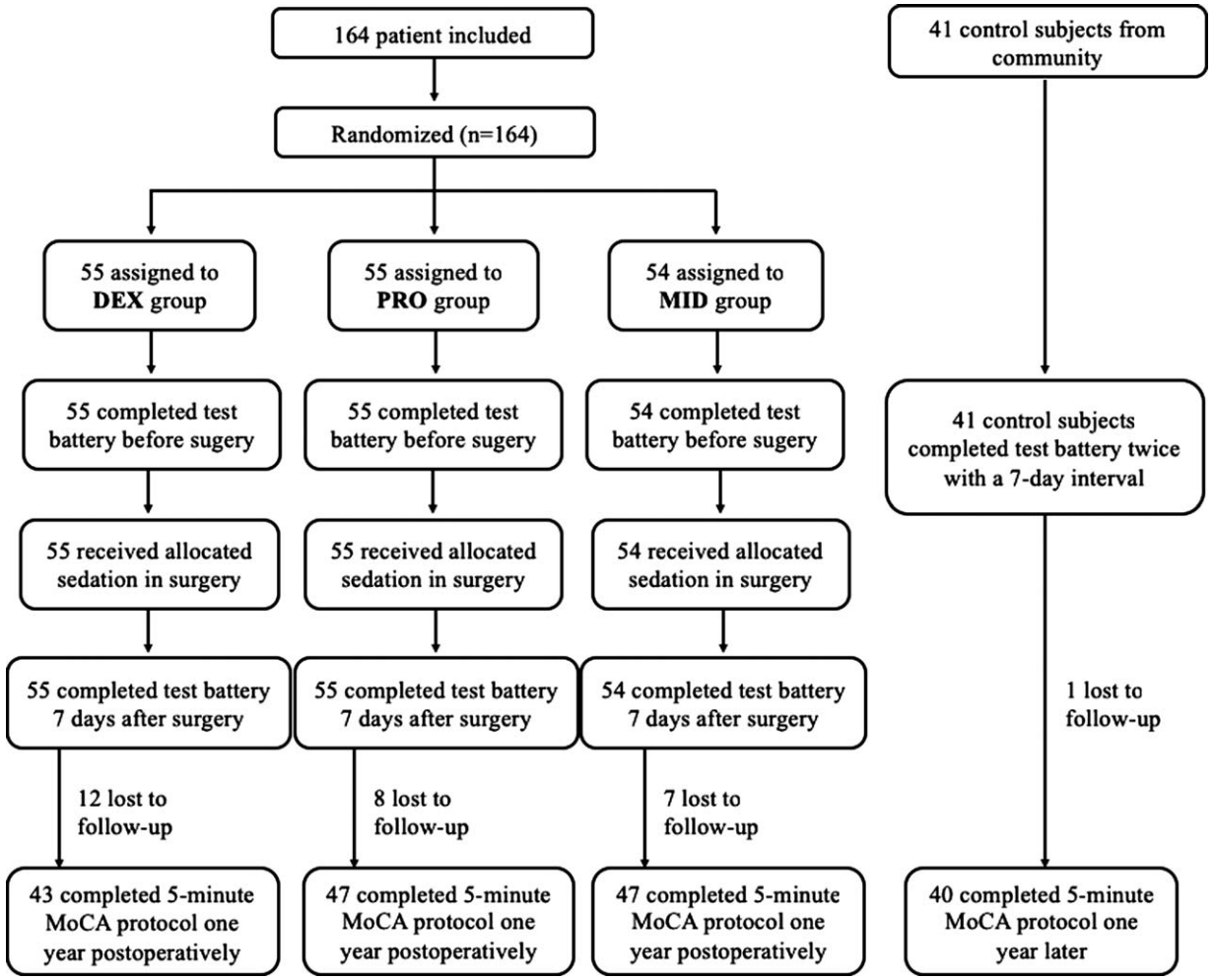

Figure 1: Flow diagram of the study. DEX: Dexmedetomidine; MID: Midazolam; MoCA: Montreal cognitive assessment; PRO: Propofol.

Table 2: Demographics and surgical characteristics of patients in DEX, PRO, and MID groups.

Parameters	DEX (n=55)	PRO (n=55)	MID (n=54)	Statistics	P
Gender (F/M)	35/20	31/24	32/22	0.613†	0.736
ASA grade					
I	4 (7.3)	2 (3.6)	2 (3.7)	2.575†	0.631
II	44 (80.0)	42 (76.4)	40 (74.1)		
III	7 (12.7)	11 (20.0)	12 (22.2)		
Age (years)	69.3±7.1	68.2±6.4	66.9±6.6	1.748*	0.177
Height (cm)	162.2±7.5	164.0±7.7	161.3±8.2	1.695*	0.187
Weight (kg)	65.4±10.2	66.3±11.5	67.9±9.2	0.814*	0.445
Education (years)	12.3±3.4	11.8±3.4	11.4±2.9	1.054*	0.351
Anesthsia time (min)	155 (125 –197.5)	165 (120.5 –196.25)	147.5 (105– 168.8)	2.781‡	0.249
Operation time (min)	105 (82.5 –145)	105 (75 –140)	90 (70 –105)	4.099‡	0.129
Fluid Input (mL)	1500 (1100–2225)	1375 (1100–2037.5)	1500 (1100–1975)	0.150*	0.939
Fluid Output (mL)	425 (150–775)	500 (200–900)	400 (150–600)	0.376*	0.829
Colloid Volume (mL)	500 (500–500)	500 (500–500)	500 (500–500)	3.828*	0.147

* F value. † χ^2 value. ‡ Kruskal-Wallis values. Data were presented as mean ± standard deviation, median (quartile), or n (%). DEX: Dexmedetomidine; F: Female; M: Male; MID: Midazolam; PRO: Propofol.

Table 3: The incidence of POCD in the experimental groups 7 days after the operation and 1 year after operation.

	Drugs				Drugs				Drugs			
Follow-up	DEX	PRO	χ^2	*P*	DEX	MID	χ^2	*P*	PRO	MID	χ^2	*P*
Seven days												
Y	22 (40.0)	10 (18.2)	6.346	0.012	22 (40.0)	28 (51.9)	1.542	0.214	10 (18.2)	28 (51.9)	13.603	<0.001
N	33 (60.0)	45 (81.8)			33 (60.0)	26 (48.1)			45 (81.8)	26 (48.1)		
One year												
Y	6 (14.0)	5 (10.6)	0.230	0.631	6 (14.0)	7 (14.9)	0.016	0.899	5 (10.6)	7 (14.9)	0.382	0.536
N	37 (86.0)	42 (89.4)			37 (86.0)	40 (85.1)			42 (89.4)	40 (85.1)		

Data were presented as *n* (%). DEX: Dexmedetomidine; MID: Midazolam; PRO: Propofol; Y indicates the number of patients with POCD. N indicates the number of patients without POCD.

Table 4: Variation of score and time spending in MoCA test before and after operation in DEX, PRO, and MID groups.

Parameters	DEX (*n*=55)	PRO (*n*=55)	MID (*n*=54)	*H**	*P*
Δ MoCA overall score	0 (0–3)	1 (−1–2)	−1 (−2–1)	8.344	0.015
Δ Trail-making time spending (s)	−7 (−19–6)	−2 (−20–11)	−2 (−17–15)	1.034	0.596
Δ Trail-making score	0	0	0	0.711	0.701
Δ Copy cube time spending (s)	0 (−6–4.5)	0 (−3–12.5)	−2 (−14–19)	1.974	0.373
Δ Copy cube score	0	0	0 (−1–0)	4.159	0.125
Δ Clock-drawing time spending (s)	−4 (−16.5–0.5)	3 (−11.8–26.0)	0 (−12–22)	5.370	0.068
Δ Clock-drawing score	0 (0–0.5)	0	0 (−1–0)	10.602	0.005

* Kruskal-Wallis value. Data are shown as median (quartile). DEX: Dexmedetomidine; MID: Midazolam; MoCA: Montreal cognitive assessment; PRO: Propofol; Δ value indicates postoperative value minus preoperative value.

Table 5: Variation of time spending and the number of correct or wrong answers in SCWT before and after operation in DEX, PRO, and MID groups.

Parameters	DEX (*n*=55)	PRO (*n*=55)	MID (*n*=54)	*H**	*P*
ΔA time (s)	−1 (−4–5)	2 (−2.0–5.0)	4 (−3.5–8.7)	1.326	0.515
ΔA correct	0	0	0	1.038	0.596
ΔA wrong	0	0	0 (−1–0)	0.884	0.643
ΔB time (s)	1 (−2.5–4)	3 (1.0–7.0)	3 (9.3–12.3)	1.593	0.451
ΔB correct	0 (0–1)	0 (0–1.0)	0 (−1–0. 5)	4.412	0.110
ΔB wrong	0 (−1–0)	0 (0 to 0)	0 (−1.5–0)	4.963	0.084
ΔC time (s)	−1 (12.8–4)	1.0 (−7–7)	−3.5 (−12.3–9.5)	1.268	0.531
ΔC correct	1 (−1–2)	−1 (−1–1)	−1 (−3–1)	9.432	0.009
ΔC wrong	0 (−1–0)	0 (−1–2)	−1 (−3–0)	4.284	0.153

* Kruskal-Wallis value. Data are shown as median (quartile). Correct: Correcting times when reading the card A or B or C; DEX: Dexmedetomidine; MID: Midazolam; PRO: Propofol; SCWT: Stroop color-word test; Time: Time spending to read the card A or B or C; Wrong: The number of wrong answers to read the card A or B or C; Δ value indicates postoperative value minus preoperative value.

Table 6: Scores obtained in digital symbol test, digital span test, and associative learning and memory test in DEX, PRO, and MID groups.

Parameters	DEX (*n*=55)	PRO (*n*=55)	MID (*n*=54)	*H**	*P*
Digital symbol test	3 (0–8)	2.0 (−3–7.0)	−2.0 (−10–6.0)	2.591	0.274
Digital span test forward	0 (−1–0)	0 (−2–1)	0 (−1– 0)	0.428	0.807
Digital span test backward	0 (−1–1)	0 (−1–0.5)	0 (−1.3–0)	3.281	0.194
Associative learning and memory test	0 (0–1)	1 (0–2)	1 (0–1)	5.783	0.055

* Kruskal-Wallis value. Data are shown as median (quartile). DEX: Dexmedetomidine; MID: Midazolam; PRO: Propofol.

Cognitive dysfunction is common after major surgery in adult patients, especially in the elderly (aged 60 years or older). The reported incidence of POCD varies depending on the patient groups included, the definition of POCD used, the tests used to establish the diagnosis and their statistical evaluation, the timing of the testing, and the choice of the control group. In this study, the overall incidence of POCD at 1 year postoperatively was 13.1%, and the incidence of POCD 1 year postoperatively was similar among the 3 experimental groups. The incidence of POCD at the third postoperative month was 12.7% as reported by Monk *et al*[20] and 17% as reported by Evered and colleagues.[21] Krenk *et al*[22] conducted a *p*rospective multicenter study to evaluate the incidence of POCD in 225 patients aged ≥60 years undergoing well-defined fast-track total hip or total knee replacement. The neuropsychological test battery they used consisted of 4 different tests, and potential cognitive dysfunction was evaluated using the z scores of 7 variables. They reported that the incidence of POCD after 1 to 2 weeks was 9.1%, but they found a similar incidence of 8.0% at 3 months postoperatively. Despite the differences in patient groups and methods, it seems that the fast-track approach in Krenk study[22] had an impact on the patients' early cognition dysfunction and led to a lower incidence of early-onset POCD.

We found that compared with the other two groups, patients in the propofol group achieved better association learning test and SCWT scores. The SCWT was used to measure the function, attention, and information processing and control of the subjects. The lower SCWT scores of the patients in the dexmedetomidine and midazolam groups indicated they had not only information processing deficits but also language impairment and executive dysfunction.[23] Thus, if patients have problems with concentration, attention and executive dysfunction, propofol might be a viable option when considering sedation.

Associative word learning tests are mainly related to the semantic memory thinking ability. The functional brain regions of associative learning and memory are mainly located in the left hemisphere, and activation of the cortex occurs in the classical left lateral fissure area.[24] In the present study, patients in the propofol group achieved better associative word learning test scores, although they have no statistical difference compared with the other two groups. Thus, the inhibitory effect of propofol on the left hemisphere language function is relatively light. A previous study demonstrated that propofol conferred differential changes in the functional connectivity of the specific and non-specific thalamocortical systems, particularly in the left hemisphere, consistent with the verbal nature of the stimuli and tasks.[25] Therefore, if elderly patients exhibit language-related problems before surgery, priority should be given to propofol sedation.

An animal experiment has shown that light propofol anesthesia for a period of 4 hours can be used as a treatment for stroke in rats to provide functional improvements.[26] The protective effects of propofol were realized by activating GABA receptors, modulating the excitatory amino acid transmitter system, and protecting brain cells against oxidative stress. Moreover, propofol can suppress apoptosis and inflammation and regulate neuroprotection-associated proteins and ion homeostasis.[27] In addition, aberrantly high levels of IL-6 and TNF-α[28] have been revealed to be closely related to POCD. Propofol has been reported to inhibit the activation and release of IL-6 and TNF-α by astrocytes in the central nervous system.[29] The above animal studies provide some evidence of the neuroprotective mechanism of propofol.

Dexmedetomidine, which is a highly selective alpha-2 adrenergic receptor agonist, is well known for its sedative and analgesic effects during the perioperative period and in critical care.[30] In recent years, several Chinese clinical studies have explored the preventive effects of dexmedetomidine on POCD in the perioperative period,[31-34] and the results revealed a significant improvement in the incidence of POCD. However, the neuropsychological test in these studies used to define POCD was a simple screening method (Mini-Mental State Examination), and there might be confounding factors due to other anesthetics used during anesthesia (*eg*, benzodiazepines, propofol, inhalation anesthetics) that could alter patients' neuropsychological states. In the present study, the anesthesia method was spinal anesthesia under light sedation with 1 sedative; moreover, the neuropsychological test battery used in this study consisted of 5 different tests focusing on different cognitive domains susceptible to dysfunction. According to our results, it seems that the incidence of POCD at POD 7 and 1 year after surgery was not better in the propofol group than the other two. However, our neuropsychological test results showed that the Δ value of the overall MoCA score and the clock-drawing score in the dexmedetomidine group was markedly higher than that in the propofol and midazolam groups. These results suggest that dexmedetomidine might have a protective effect on some cognitive functions, especially in terms of visuospatial abilities.

A study has revealed that midazolam administration increases the risk of POCD in elderly patients.[35] We also found that midazolam sedation led to a higher incidence of POCD than did dexmedetomidine and propofol 7 days after surgery.

Hypotension during surgery is the main risk factor for POCD. Hypotension is the simplest and most common cause of cerebral hypoperfusion and decreased cerebral flow, and the latter has been considered an important risk factor for POCD in most early studies.[36] In the present study, we collected data regarding the duration of hypotension and the type and dose of administered vasoactive drugs. The results showed no significant differences in these variables among the 3 groups. Thus, the vasoactive drugs used to be treatment hypotension during surgery had no effect on the occurrence of POCD in the 3 experimental groups.

Pain is also considered a risk factor for POCD as the areas of the brain involved in pain perception and cognitive control overlap.[37] The patients in all 3 sedative groups achieved pain control with PCEA pain management. Additionally, patients in the 3 groups showed similar

postoperative NRS scores with few complications. Thus, the good pain management method used in this study minimally contributed to the occurrence of POCD in the 3 groups.

This study was conducted at a single institution on a homogeneous group of patients. Therefore, it is unclear whether the results are generalizable to other patient populations, procedures, and institutions. However, we designed the study to maximize the reliability of the neurocognitive and functional test results and limit confounders. Furthermore, several patients received blood transfusion during surgery, which can affect neurocognitive test scores.[38] However, the number of patients receiving blood transfusion was too small for statistical analysis.

In conclusion, among dexmedetomidine, propofol and midazolam sedation in elderly patients, propofol influences cognitive function slightly, while midazolam impairs it the most. The effect on POCD in elderly patients 1 year after arthroplasty was independent of the sedative type.

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Conflicts of interest

None.

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