Intelligent Anesthesia

Article

Effect of dexmedetomidine on neurological and cognitive functions and inflammatory factor expression in elderly patients undergoing knee arthroplasty

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Abstract

Background: Total knee arthroplasty (TKA) in elderly patients with osteoarthritis can lead to inflammation and postoperative cognitive dysfunction (POCD). Dexmedetomidine may reduce these adverse effects, but the optimal dosage to minimize postoperative complications is still under investigation.

Objective: This study aims to investigate the effects of dexmedetomidine on neurological function, cognitive function, and inflammatory factor expression in elderly patients undergoing knee arthroplasty.

Methods: A total of 120 elderly patients who underwent unilateral total knee arthroplasty (TKA) from March 2022 to March 2023 were enrolled and divided randomly into four groups (A, B, C, D), each with 30 patients. Group A received combined spinal-epidural anesthesia, while groups B, C, and D received additional dexmedetomidine at a loading dose of 0.5 μg/kg, followed by continuous intravenous infusion at rates of 0.30, 0.50, and 0.80 μg/(kg·h), respectively. Serum levels of inflammatory factors, markers of brain tissue injury, and Montreal Cognitive Assessment Scale (MoCA) scores were compared before and after surgery among the groups. Postoperative cognitive dysfunction (POCD) and adverse events were also recorded.

Results: Serum TNF-α, IL-6, and IL-10 levels in all groups were higher at 1 hour, 1 day, and 3 days post-surgery than pre-surgery ($P < 0.05$). Serum S-100β and ICAM-1 levels increased post-surgery in all groups but were significantly lower in group D than in groups A, B, and C, and lower in group C than in groups A and B ($P < 0.05$). MoCA scores in groups A and B at 1, 3, and 7 days post-surgery were lower than pre-surgery ($P < 0.05$). MoCA scores in groups C and D decreased at 1 and 3 days post-surgery but returned to preoperative levels by day 7. MoCA scores in group D were higher than those in groups A, B, and C at 1, 3, and 7 days post-surgery, and higher in group C than in groups A and B ($P < 0.05$). The incidence of POCD on day 3 post-surgery was lower in group D than in groups A and B and lower in group C than in group A ($P < 0.05$). There was no significant difference in hypotension or bradycardia among the four groups ($P > 0.05$).

Conclusions: Continuous intraoperative infusion of dexmedetomidine at a rate of 0.80 μg/(kg·h) significantly reduces postoperative inflammatory, neurological, and cognitive injuries in elderly patients undergoing knee arthroplasty, ensuring anesthesia safety.

Trial registration: Not applicable.

Keywords: Dexmedetomidine; Anesthesia; Knee arthroplasty; Tumor necrosis factor-alpha; Interleukin-6; Cell adhesion molecule-1; Astrocyte-derived protein; Cognitive dysfunction

Introduction

Knee osteoarthritis is a degenerative joint disease primarily affecting the elderly. Total knee arthroplasty (TKA) is often performed to treat severe cases, but this invasive procedure can trigger a significant inflammatory response and stress reaction due to the implantation of prosthetic materials, potentially leading to neuronal damage and postoperative cognitive dysfunction (POCD). Combined spinal-epidural anesthesia is commonly used due to its effective muscle relaxation and rapid

onset, yet postoperative stress responses may persist, and it has limited effects on alleviating patient anxiety, increasing the risk of central nervous complications post-surgery.

Dexmedetomidine, known for its protective effects on the cardiovascular system, can mitigate the neurotoxic effects of anesthetics, reduce neuronal apoptosis, and lower the incidence of POCD. However, there is currently no standardized clinical dosage for dexmedetomidine. Research is ongoing to evaluate whether increasing the dexmedetomidine dose can further reduce postoperative inflammatory, neurological, and cognitive injuries.

This study evaluates the effects of different doses of dexmedetomidine on inflammatory response, neuronal injury, and cognitive function in elderly patients undergoing TKA.

Methods

Patient Selection

This prospective study included 120 elderly patients who underwent elective unilateral TKA from March 2022 to March 2023 at Hebei PetroChina Central Hospital. Patients were randomly divided into four groups: A, B, C, and D, each with 30 participants. Gender, age, BMI, disease duration, education level, surgery time, ASA classification, affected side, and intraoperative blood loss were comparable among groups ($P > 0.05$).

Table 1. Comparison of general information among four groups

General Information	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	Group D (n = 30)
Gender [n (%)]				
Male	16 (53.33%)	18 (60.00%)	20 (66.67%)	19 (63.33%)
Female	14 (46.67%)	12 (40.00%)	10 (33.33%)	11 (36.67%)
Age ($\bar{x} \pm s$, years)	67.36 ± 2.30	66.98 ± 1.99	67.71 ± 2.27	68.02 ± 2.31
BMI ($\bar{x} \pm s$, kg/mb)	25.16 ± 0.64	25.31 ± 0.61	25.25 ± 0.54	24.99 ± 0.49
Education Level [n (%)]				
No Education	4 (13.33%)	1 (3.33%)	2 (6.67%)	4 (13.33%)
Elementary	12 (40.00%)	11 (36.67%)	13 (43.33%)	9 (30.00%)
Middle School	6 (20.00%)	8 (26.67%)	8 (26.67%)	5 (16.67%)
High School and Above	8 (26.67%)	10 (33.33%)	7 (23.33%)	12 (40.00%)
Disease Duration ($\bar{x} \pm s$, years)	8.52 ± 2.62	9.04 ± 3.01	8.96 ± 2.50	8.75 ± 2.33
ASA Classification [n (%)]				
I	18 (60.00%)	20 (66.67%)	17 (56.67%)	21 (70.00%)
II	12 (40.00%)	10 (33.33%)	13 (43.33%)	9 (30.00%)
Affected Side [n (%)]				
Left Knee	14 (46.67%)	12 (40.00%)	13 (43.33%)	11 (36.67%)
Right Knee	16 (53.33%)	18 (60.00%)	17 (56.67%)	19 (63.33%)
Intraoperative Blood Loss ($\bar{x} \pm s$, mL)	232.15 ± 10.36	234.08 ± 11.13	236.25 ± 9.65	235.98 ± 10.08
Surgery Duration ($\bar{x} \pm s$, h)	3.35 ± 0.38	3.41 ± 0.40	3.38 ± 0.42	3.43 ± 0.36

Group A received spinal-epidural anesthesia; Groups B, C, and D received additional continuous intravenous dexmedetomidine infusions at 0.30, 0.50, and 0.80 μg/(kg·h), respectively, after achieving fixed anesthetic levels. ASA: American Society of Anesthesiologists.

Table 2. Comparison of serum inflammatory factors before and after surgery among four groups

Group	n	Time	TNF-α (pg/mL)	IL-10 (ng/L)	IL-6 (pg/mL)
A	30	Preoperative	23.08 ± 4.27	143.62 ± 26.57	63.62 ± 7.52
		1h Postop	56.25 ± 3.97[a]	232.57 ± 31.20[a]	242.59 ± 25.62[a]
		1d Postop	45.74 ± 4.63[a]	195.33 ± 16.52[a]	196.58 ± 22.16[a]
		3d Postop	36.38 ± 3.75[a]	173.28 ± 15.26[a]	132.65 ± 16.58[a]
B	30	Preoperative	22.96 ± 5.10	139.69 ± 24.10	65.10 ± 8.10
		1h Postop	54.79 ± 5.10[a]	227.63 ± 27.53[a]	236.79 ± 31.40[a]
		1d Postop	43.96 ± 5.46[a]	188.78 ± 12.18[a]	187.27 ± 19.37[a]
		3d Postop	34.24 ± 4.69[a]	169.46 ± 12.75[a]	129.78 ± 17.96[a]
C	30	Preoperative	20.75 ± 3.98	141.28 ± 19.86	62.96 ± 6.66
		1h Postop	42.16 ± 4.63[abc]	185.49 ± 28.12[abc]	186.27 ± 22.18[abc]
		1d Postop	34.05 ± 3.75[abc]	171.63 ± 15.37[abc]	123.57 ± 20.74[abc]
		3d Postop	28.10 ± 4.06[abc]	153.71 ± 10.89[abc]	83.26 ± 12.45[abc]
D	30	Preoperative	21.52 ± 4.33	138.76 ± 22.52	63.18 ± 6.75
		1h Postop	38.52 ± 6.18[abcd]	172.56 ± 22.79[abcd]	172.28 ± 25.16[abcd]
		1d Postop	30.29 ± 4.59[abcd]	163.59 ± 11.98[abcd]	112.46 ± 18.56[abcd]
		3d Postop	24.33 ± 3.45[abcd]	140.55 ± 13.24[abcd]	71.51 ± 14.76[abcd]

Group A received spinal-epidural anesthesia. Groups B, C, and D received an additional dexmedetomidine loading dose of 0.5 μg/kg after level fixation, with continuous intravenous infusion of dexmedetomidine at 0.30, 0.50, and 0.80 μg/(kg·h) during surgery, respectively.

TNF-α: Tumor Necrosis Factor-α, IL-10: Interleukin-10, IL-6: Interleukin-6.

[a]: Compared to preoperative values, $P < 0.05$.

[b]: Compared to Group A at the same time point, $P < 0.05$.

[c]: Compared to Group B at the same time point, $P < 0.05$.

[d]: Compared to Group C at the same time point, $P < 0.05$.

Inclusion criteria included a confirmed diagnosis of knee osteoarthritis, eligibility for elective TKA, age between 60 and 75, acceptance of combined spinal-epidural anesthesia, and an ASA classification of I or II. Patients with severe liver or kidney dysfunction, hematologic or cerebrovascular diseases, psychiatric disorders, or allergies to the study medications were excluded.

Anesthesia Protocol

After IV access was established, patients were given supplemental oxygen and monitored for vital signs. Group A received combined spinal-epidural anesthesia with 0.75% ropivacaine, while groups B, C, and D received additional dexmedetomidine. After a loading dose of 0.5 μg/kg, dexmedetomidine was administered via continuous IV infusion at rates of 0.30, 0.50, and 0.80 μg/(kg·h), respectively, starting after stable fixation of the anesthesia plane.

Postoperative analgesia was provided through IV self-controlled analgesia using a solution of 1% ropivacaine, sufentanil, and tropisetron in saline.

Observational Indicators

Inflammatory factor levels: Serum samples were collected at baseline, 1 hour, 1 day, and 3 days post-surgery to assess levels of TNF-α, IL-6, and IL-10 via ELISA.

Markers of brain injury: Levels of ICAM-1 and S-100β were measured in serum samples to evaluate brain tissue damage.

Cognitive function: Cognitive status was assessed using the Montreal Cognitive Assessment Scale (MoCA) on days 1, 3, and 7 post-surgery. MoCA evaluates multiple cognitive domains, with scores adjusted for education level.

POCD and adverse events: Incidences of POCD (MoCA <27), hypotension, and bradycardia were

recorded for each group on days 3 and 7 post-surgery.

Statistical Analysis

Data were analyzed using SPSS 22.0. Quantitative data were expressed as mean ± standard deviation, with comparisons among groups performed using ANOVA and paired t-tests. Categorical data were expressed as percentages, and chi-square tests were used for comparisons. A significance level of $\alpha = 0.05$ was applied.

Table 3. Comparison of brain tissue injury markers before and after surgery among four groups

Group	n	Marker	Preoperative	1h Postoperative	1d Postoperative	3d Postoperative
A	30	S-100β (μg/L)	1.20 ± 0.23	2.78 ± 0.36[a]	2.32 ± 0.40[a]	2.01 ± 0.35[a]
		ICAM-1 (ng/mL)	425.36 ± 52.27	842.58 ± 63.29[a]	715.54 ± 54.29[a]	625.29 ± 49.18[a]
B	30	S-100β (μg/L)	1.19 ± 0.26	2.69 ± 0.41[a]	2.27 ± 0.32[a]	1.93 ± 0.29[a]
		ICAM-1 (ng/mL)	418.67 ± 48.96	827.67 ± 57.18[a]	687.69 ± 60.12[a]	586.75 ± 52.27[a]
C	30	S-100β (μg/L)	1.21 ± 0.25	2.24 ± 0.35[abc]	1.96 ± 0.29[abc]	1.62 ± 0.31[abc]
		ICAM-1 (ng/mL)	423.59 ± 53.28	754.28 ± 60.21[abc]	576.54 ± 48.67[abc]	501.62 ± 46.29[abc]
D	30	S-100β (μg/L)	1.20 ± 0.18	1.96 ± 0.28[abcd]	1.70 ± 0.33[abcd]	1.43 ± 0.24[abcd]
		ICAM-1 (ng/mL)	416.77 ± 47.62	710.27 ± 53.24[abcd]	519.48 ± 52.64[abcd]	462.33 ± 53.20[abcd]

Group A received spinal-epidural anesthesia. Groups B, C, and D received an additional dexmedetomidine loading dose of 0.5 μg/kg after level fixation, with continuous intravenous infusion of dexmedetomidine at 0.30, 0.50, and 0.80 μg/(kg·h) during surgery, respectively.

ICAM-1: Intercellular Adhesion Molecule-1, S-100β: astrocyte-derived protein.

[a]: Compared to preoperative values, $P < 0.05$.

[b]: Compared to Group A at the same time point, $P < 0.05$.

[c]: Compared to Group B at the same time point, $P < 0.05$.

[d]: Compared to Group C at the same time point, $P < 0.05$.

Results

Inflammatory Factors

Preoperative inflammatory factor levels showed no significant differences among groups ($P > 0.05$). However, TNF-α, IL-6, and IL-10 levels at 1 hour, 1 day, and 3 days post-surgery were significantly lower in group D compared to groups A, B, and C, and lower in group C compared to groups A and B ($P < 0.05$).

Brain Injury Markers

ICAM-1 and S-100β levels were significantly elevated post-surgery across all groups but were consistently lower in group D than in groups A, B, and C, and lower in group C than in groups A and B ($P < 0.05$).

Table 4. Comparison of MoCA scores before and after surgery among four groups

Group	n	Preoperative	1 Day Postoperative	3 Days Postoperative	7 Days Postoperative

A	30	28.12 ± 1.62	21.68 ± 1.57[a]	23.65 ± 1.38[a]	25.89 ± 1.26[a]
B	30	27.96 ± 1.38	22.14 ± 1.39[a]	24.03 ± 1.40[a]	26.10 ± 1.30[a]
C	30	28.24 ± 1.43	24.86 ± 1.74[abc]	25.97 ± 1.24[abc]	27.68 ± 1.11[bc]
D	30	28.43 ± 1.50	25.92 ± 1.56[abcd]	26.49 ± 1.33[abcd]	28.30 ± 1.03[bcd]

Group A received spinal-epidural anesthesia. Groups B, C, and D received an additional dexmedetomidine loading dose of 0.5 μg/kg after level fixation, with continuous intravenous infusion of dexmedetomidine at 0.30, 0.50, and 0.80 μg/(kg·h) during surgery, respectively.

MoCA: Montreal Cognitive Assessment

[a]: Compared to preoperative values, $P < 0.05$.

[b]: Compared to Group A at the same time point, $P < 0.05$.

[c]: Compared to Group B at the same time point, $P < 0.05$.

[d]: Compared to Group C at the same time point, $P < 0.05$.

Table 5. Comparison of POCD and incidence of adverse reactions before and after surgery among four groups

Group	n	3-days POCD	7-days POCD	Hypotension	Bradycardia
A	30	14 (46.67)	8 (26.67)	2 (6.67)	1 (3.33)
B	30	12 (40.00)	7 (23.33)	1 (3.33)	2 (6.67)
C	30	6 (20.00)[a]	3 (10.00)[a]	3 (10.00)	2 (6.67)
D	30	3 (10.00)[ab]	1 (3.33)[ab]	8 (26.67)	6 (20.00)

Group A received spinal-epidural anesthesia. Groups B, C, and D received an additional dexmedetomidine loading dose of 0.5 μg/kg after level fixation, with continuous intravenous infusion of dexmedetomidine at 0.30, 0.50, and 0.80 μg/(kg·h) during surgery, respectively.

POCD: Postoperative Cognitive Dysfunction

[a]: Compared to Group A, $P < 0.05$.

[b]: Compared to Group B, $P < 0.05$.

Cognitive Function (MoCA Scores)

MoCA scores in groups A and B were significantly lower than preoperative levels at days 1, 3, and 7 post-surgery. Groups C and D showed similar declines at days 1 and 3 but returned to baseline by day 7. MoCA scores were higher in group D than in groups A, B, and C, and higher in group C than in groups A and B at all postoperative time points ($P < 0.05$).

POCD and Adverse Events

On day 3 post-surgery, POCD incidence was significantly lower in group D compared to groups A and B, and lower in group C than in group A ($P < 0.05$). There were no significant differences in hypotension or bradycardia incidence among the groups ($P > 0.05$).

Discussion

Total knee arthroplasty (TKA) is a traumatic surgery for treating degenerative knee disease in the elderly, commonly performed under combined spinal-epidural anesthesia (3). However, surgical trauma, advanced age, and insufficient sedation or analgesia may contribute to postoperative cognitive dysfunction (POCD) (11-12). Reducing POCD incidence post-TKA in elderly patients has become a significant clinical challenge. Studies show that dexmedetomidine provides effective sedation and analgesia, reducing POCD occurrence in elderly patients, though the optimal dose is still under investigation (13-14). Research by Fan Yuhong et al. found that continuous infusion at rates of 0.50 and 0.80 μg/kg per hour mitigated inflammatory responses and lowered POCD rates in elderly patients (11). Similarly, Wang Haili et al. reported that 0.50 μg/kg dexmedetomidine stabilized hemodynamic levels during anesthesia in elderly hip replacement patients, reducing cognitive impairment with reliable safety (12). Peng Bei's study also demonstrated that 0.30 μg/kg continuous infusion reduced POCD rates in elderly hip replacement patients (15). Therefore, this study compares dexmedetomidine continuous infusion

doses of 0.30, 0.50, and 0.80 μg/(kg·h) with standard anesthesia (Group A) to assess efficacy.

Our findings indicate that dexmedetomidine effectively reduces postoperative neurological and cognitive injuries in elderly TKA patients, with the 0.80 μg/kg per hour infusion achieving the best results. This may be due to dexmedetomidine's stimulation of α receptors on arterioles and pial arteries, leading to vascular constriction, reduced local blood flow, and improved cerebral oxygenation. This protective effect on brain tissue may also be linked to its activation of PI3K/Akt and inhibition of the p38/MAPK signaling pathways, as well as increased expression of brain-derived neurotrophic factor (BDNF) through the JAK/STAT pathway, which collectively mitigates cognitive impairment (16-17). Higher doses of dexmedetomidine demonstrate stronger effects and more significant improvements (18-20).

Additionally, dexmedetomidine significantly reduces postoperative inflammatory responses in elderly TKA patients, particularly with the 0.80 μg/(kg·h) infusion, consistent with Fan Yuhong's findings (11). This effect is likely due to dexmedetomidine's inhibition of excessive macrophage activation, reducing inflammatory cytokine release and controlling inflammation-related damage, with evidence suggesting that higher doses correlate with better anti-inflammatory effects (21-22). In our study, both 0.50 and 0.80 μg/(kg·h) infusions lowered POCD rates, with the 0.80 μg/(kg·h) dose proving most effective. Inflammatory cytokines are a known risk factor for POCD, and the superior anti-inflammatory and neuroprotective effects of the 0.80 μg/(kg·h) dose likely contribute to reduced POCD incidence (23-25).

However, the 0.80 μg/(kg·h) dose was associated with an increased incidence of hypotension and bradycardia, possibly due to dexmedetomidine's suppressive effects on sinoatrial and atrioventricular node functions, potentially prolonging recovery time and triggering hypotension and bradycardia (26). These adverse effects primarily occurred during post-surgery tourniquet release and were effectively managed with atropine or ephedrine, with no significant differences between groups, potentially due to the small sample size in this study.

Despite analyzing different dexmedetomidine doses, limitations include a small sample size and exclusion of patients over 75 with comorbidities who rarely undergo surgery, which may affect results. Further studies are needed to determine if the neuroprotective effects of dexmedetomidine in the elderly are age dependent.

In conclusion, continuous intravenous infusion of 0.80 μg/(kg·h) dexmedetomidine effectively reduces inflammatory, neurological, and cognitive injuries and lowers POCD rates in elderly TKA patients, ensuring clinical anesthesia safety.

Conflicts of Interest:

The authors declare that they have no competing interests.

Abbreviations

Akt: protein kinase B
ANOVA: analysis of variance
ASA: American society of anesthesiologists
BDNF: brain-derived neurotrophic factor
BMI: body mass index
ELISA: enzyme-linked immunosorbent assay
ICAM-1: intercellular adhesion molecule-1
IL-6: interleukin-6
IL-10: interleukin-10
IV: intravenous
JAK/STAT: Janus kinase/signal transducer and activator of transcription
MAPK: mitogen-activated protein kinase
MoCA: Montreal cognitive assessment scale
PI3K: phosphoinositide 3-kinase
POCD: postoperative cognitive dysfunction
S-100β: S-100 beta protein
SPSS: statistical package for the social sciences
TKA: total knee arthroplasty
TNF-α: tumor necrosis factor-alpha

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