Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Effects of Dexmedetomidine on Postoperative Quality of Recovery and Electroencephalogram in Elderly Patients Undergoing Total Knee Arthroplasty: A Randomized Clinical Trial

Hao Zhang*, Yang Gao*, Deng Liu*, Wenhui Lyu, Xinyi Xing, Ziqing He, Lei Wang, Lei Zhang, Lijian Chen

Department of Anesthesiology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, 230022, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lijian Chen; Lei Zhang, Department of Anesthesiology, the First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei, 230022, People's Republic of China, Tel +8613966699467; +8613966745097, Email chenlijian77@126.com; zhlanesth@yeah.net

Purpose: Anesthesia management strategies in elderly patients undergoing total knee arthroplasty (TKA) are critical to the postoperative quality of recovery (QoR), and changes in electroencephalogram (EEG) associated with anesthesia drugs may play an important role in this process. This study aimed to determine the effects of different doses of dexmedetomidine on postoperative QoR in elderly TKA patients, and whether there is a correlation with specific EEG changes.

Methods: In this randomized controlled trial, elderly patients (aged ≥ 60 years) undergoing elective TKA were randomly allocated in a 1:1:1 ratio to 0.6 μg/kg/h dexmedetomidine (Group D2), 0.3 μg/kg/h dexmedetomidine (Group D1) and saline (Group N). On postoperative days 1 and 3, the15-item Quality of Recovery (QoR-15) scale was used to evaluate the postoperative recovery of patients among the three groups. Perioperative EEG data were also recorded.

Results: The difference of QoR-15 scores on postoperative day 1 was significant for Group D2 vs Group N (126 [123–129] points vs 120 [116–123] points; median difference, 6 points [95% CI, 4 to 8]; $P < 0.001$) and Group D2 vs Group D1 (126 [123–129] points vs 122 [118–126]; median difference, 4 points [95% CI, 2 to 5]; $P = 0.001$), but not for Group D1 vs Group N. However, no significant difference was observed in the global and dimensional QoR-15 scores on postoperative day 3 among the three groups. Intraoperative EEG power spectra analysis revealed a decrease in α oscillation peak power and an increase in slow oscillation peak power in Group D1 and Group D2, compared with Group N. In addition, the slow oscillation peak power exhibited weak positive correlations with QoR-15 scores on postoperative day 1 ($r = 0.319$, $P < 0.001$).

Conclusion: A loading dose of dexmedetomidine (0.5 μg/kg) infused within 10 minutes before anesthesia induction, followed by a maintenance at 0.6 μg/kg/h, improved QoR-15 on postoperative day 1 in elderly TKA patients, which may be partly related to the fact that dexmedetomidine deepens anesthesia by increasing the slow oscillation peak power in the appropriate range.

Keywords: dexmedetomidine, quality of recovery, electroencephalogram, aged, total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) is known to be the most effective treatment for knee pain in patients with osteoarthritis or rheumatic arthritis.[1] It is also an extensive and complex procedure that is prone to postoperative complications. Furthermore, the elderly patients are sensitive to operation-induced stress due to significant reductions in organ reserve and compensatory capacity, and often experience early postoperative complications, such as pain, sleep disturbances and anxiety,[2,3] which could seriously affect the quality of recovery (QoR). How to improve postoperative life quality and perform functional exercises as early as possible in elderly patients remains an important challenge and a hot issue of concern for clinicians.[4]

Received: 23 April 2025
Accepted: 21 August 2025
Published: 29 August 2025

Dexmedetomidine is a highly selective α-2 adrenergic agonist with dose-dependent sedative, analgesic and anti-inflammatory effects.[5] Perioperative application of dexmedetomidine may benefit in mitigating surgical stress and inflammatory response, improving N3 sleep in a dose-dependent manner,[6–10] and has been shown to improve postoperative QoR in adult patients during various surgeries.[7,11–15] However, the effect of dexmedetomidine on the QoR after TKA in the elderly and the mechanisms involved have not been fully elucidated.

Furthermore, dexmedetomidine is clinically infused in a wide range of rates and electroencephalogram (EEG) characteristics varied with doses. When infused with dexmedetomidine at a low dose, the EEG is characterized by spindle oscillation,[16] which is a general term for spindle-like activity (12–16 Hz oscillation, lasting 1–2 seconds) and slow-wave activity during dexmedetomidine-induced sedation. Purdon et al showed that the higher the rate of dexmedetomidine infusion, the greater the amplitude of slow oscillations.[17] We previously demonstrated that dexmedetomidine can enhance propofol or sevoflurane anesthesia, while increasing slow-wave power and decreasing the frequency of each brain wave segment.[18,19] However, the dose-response data of dexmedetomidine and its EEG-recovery correlation in elderly TKA patients remain unclear.

This study aimed to explore the effects of different doses of dexmedetomidine on postoperative QoR in elderly patients undergoing TKA. An additional purpose of the study was to preliminarily investigate whether there is an association between the EEG changes induced by dexmedetomidine and postoperative QoR.

Materials and Methods

Study Setting and Population

Ethical approval for this study (Approval number: PJ 2022–13-12) was provided by the Ethical Committee of the First Affiliated Hospital of Anhui Medical University on 9 November 2022. This study has been registered at Chinese Clinical Trial Registry (ChiCTR2200066337) on 1 December 2022. This single-center randomized clinical trial was performed at a tertiary hospital in China between December 2022 and June 2023. The study was conducted in adherence to the principles outlined in the Declaration of Helsinki and written informed consent for study participation was obtained from all patients before enrollment. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[20] Patients aged 60 years or older undergoing elective TKA with American Society of Anesthesiologists (ASA) physical status 1 to 3 were eligible to participate. Exclusion criteria included serious bradycardia (resting heart rate [HR] < 50 bpm), allergy to trial-related medications, severe hepatic or renal dysfunction, dementia or treatment with antipsychotic agents and inability to complete scale assessment.

Randomization and Blinding

Eligible patients were randomly divided on a 1:1:1 ratio into three groups: low-dose dexmedetomidine group (Group D1), high-dose dexmedetomidine group (Group D2), and normal saline group (Group N). A randomized sequence was generated using random numbers from the SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA). A researcher who was not involved in the study prepared the study agents in identical 50 mL syringes based on the treatment protocol information contained within sequentially numbered sealed envelopes. The patients, investigators, responsible anesthesiologists, surgeons, and scale assessors were blinded to the intervention throughout the study period.

To minimize potential bias during EEG analysis, a rigorous blinding procedure was implemented. The analysts remained blinded to group allocation, clinical outcomes, and perioperative variables throughout feature extraction, quantitative EEG analysis, and statistical interpretation.

Protocol and Intervention

During the preoperative assessment, we collected baseline data include demographic characteristics, diseases history and QoR scores. Standard monitoring was initiated upon arrival in the operating room, which included electrocardiography, HR, pulse oxygen saturation (SpO_2), mean arterial pressure (MAP) and end-tidal carbon dioxide partial pressure ($ETCO_2$). A four-channel sensor was attached to specific locations on the patient's forehead: Fp1, Fp2, F7, and F8; earth electrode at Fpz; reference electrode approximately 1 cm above Fpz. For each electrode, impedance was maintained

below 5 kΩ. Frontal EEG data, including patient state index (PSI), were recorded using a Sedline® brain function monitor (Masimo Corporation, Irvine, CA, USA)[21] at a sampling rate of 178 Hz.

Considering that elderly patients are often received anticoagulant therapy, accompanied by hyperostosis and narrow intervertebral space, it is unsuitable or difficult to obtain epidural puncture. In addition, with the decline of organ function reserve, intraspinal anesthesia is prone to cause significant hemodynamic fluctuations due to sympathetic block. Therefore, general anesthesia combined with nerve block is the preferred anesthesia for elderly patients undergoing TKA in our institution.

Patients in Group D1 and Group D2 received a loading dose of dexmedetomidine (0.5 μg/kg) within 10 minutes before anesthesia induction, followed by continuous pumping of dexmedetomidine at 0.3 μg/kg/h and 0.6 μg/kg/h, respectively. The specific dose of dexmedetomidine was determined by referring to previous similar studies[22,23] and considering the decreased tolerance and increased sensitivity to the drug in elderly patients. Correspondingly, patients in Group N were administered an equivalent volume of normal saline infused at the same rates. Intravenous anesthesia was induced using propofol (1.5–2.0 mg/kg) and sufentanil (0.2–0.4 μg/kg). When the PSI decreased below 50, cisatracurium (0.2 mg/kg) was administered. Assisted breathing was performed for 3 minutes, and then laryngeal mask airway was inserted and mechanical ventilation was performed. Then, ultrasound-guided femoral nerve block (0.33% ropivacaine 15–20 mL) and sciatic nerve block (0.33% ropivacaine 20–25 mL) were performed following the experienced anesthesiologists.

During anesthesia maintenance, propofol and remifentanil were continuously administered at 3–6 mg/kg/h and 0.05–0.2 μg/kg/min, respectively. The propofol infusion dose was increased or decreased on a gradient of 0.3 mg/kg/h each time to maintain a PSI of 25–50. Flurbiprofen (50 mg) and local infiltration analgesia with ropivacaine (100 mg, 10 mL) and NaCl (0.9%, 10 mL) were administered before incision closure. Intraoperative vasoactive drugs were applied to maintain MAP within ± 20% of the baseline and HR within 50–100 bpm.

After the operation, all patients were transferred to the post-anesthesia care unit (PACU) for recovery. The laryngeal mask was removed once the patient regained consciousness from anesthesia and demonstrated adequate tidal volume and stable hemodynamic parameters. Nurses assessed pain at rest using numerical rating scale (NRS) every 5 minutes during the PACU. Patients with NRS score ≥ 4 received sufentanil 0.1 μg/kg as needed. When the vital signs were stable and the Steward recovery score was > 4, the patients were transferred to the general ward for standardized postoperative care and rehabilitation.[24]

With strict adherence to drug use contraindications, attending physicians used multimodal nonsteroidal internal analgesics and opioids to maintain NRS scores < 4 and followed structured criteria:[25–27] For patients with NRS ≥ 4, oral selective cyclooxygenase-2 (COX-2) inhibitors are preferred; If oral administration is not convenient, intravenous flurbiprofen axetil or intramuscular diclofenac sodium lidocaine injection can be selected. When the NRS score ≥ 7, opioid analgesics were added. Oral oxycodone was the first choice. Tramadol intramuscular injection was given if adverse reactions such as intractable vomiting occurred. Transdermal patches, including transdermal buprenorphine and transdermal fentanyl, were used as needed if contraindications to tramadol, such as convulsions, occurred. This multimodal regimen follows the principle of balanced analgesia with optimized efficacy and safety.

Data Collection

The primary outcome was the difference in QoR scores on postoperative day 1 (POD1) measured by the 15-item Quality of Recovery (QoR-15) scales,[28] which designed to evaluate five dimensions: physical comfort, physical independence, psychological support, pain and emotional state. The total score ranges from 0 (poorest QoR) to 150 (best QoR).

The secondary outcome was perioperative EEG analysis. We further assessed the relationship between the characteristics of EEG waveforms and QoR-15 scores on POD1. In addition, QoR-15 scores on POD3, the type and dose of analgesics used on POD1, incidence of intraoperative tourniquet hypertension,[29,30] changes in perioperative MAP, HR, and PSI values, the administration of vasoactive drugs and intraoperative adverse events (including hypotension, hypertension and bradycardia) were recorded.

Sample Size and Statistical Analysis

A difference of 6 points in the QoR-15 scores for perioperative interventions was recently recommended as a minimum clinically important difference.[31] Based on pre-pilot data, the average QoR-15 scores on POD1 for Group N, Group D1, and

Group D2 were 118, 123, and 128, respectively. And standard deviation (SD) within the group were 7, 6 and 2, respectively. Setting an α of 0.017 (two sided),[32] a test efficacy of 0.9 and a dropout rate of 10%, we planned to enroll 225 patients.

The Shapiro–Wilk test was employed to confirm the normality of the data. Interval data were expressed as mean ± SD or median (interquartile range) depending on the normality of the data and compared using one-way analysis of variance or Kruskal–Wallis test. Categorical variables were expressed as numbers and percentages and compared using the Pearson χ^2 test. The P value was adjusted according to Bonferroni post hoc testing and fixed at 0.017 for pairwise comparison. The median difference and 95% confidence interval (CI) on primary outcomes were calculated to analyze the effect of dexmedetomidine on improving the QoR after TKA.

The EEG data were processed using MATLAB 2021b (The MathWorks, Natick, MA, USA).[21] Based on the information obtained from the EEG power spectrum analysis, a segment of consecutive 120-seconds EEG data was selected and the power spectrum was computed by the multi-taper spectral estimation method implemented by the Chronux toolbox.[33] Concurrently, frontal spectrograms were generated from the EEG data of representative patients in each group for comparison. And we calculated the α and slow oscillatory peak power for each patient. Linear regression analyses were used to explore the relationship between QoR-15 scores on POD1 and EEG waveforms. All statistical analyses were conducted using SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA) and 2-sided $P < 0.05$ were considered statistically significant.

Results

Demographic and Clinical Characteristics of the Patients

From December 2022 to June 2023, of 285 patients screened for eligibility, 225 were enrolled and randomly assigned to one of the three groups (75 patients per group) (Figure 1). Twelve patients who were lost to follow-up were excluded and nine

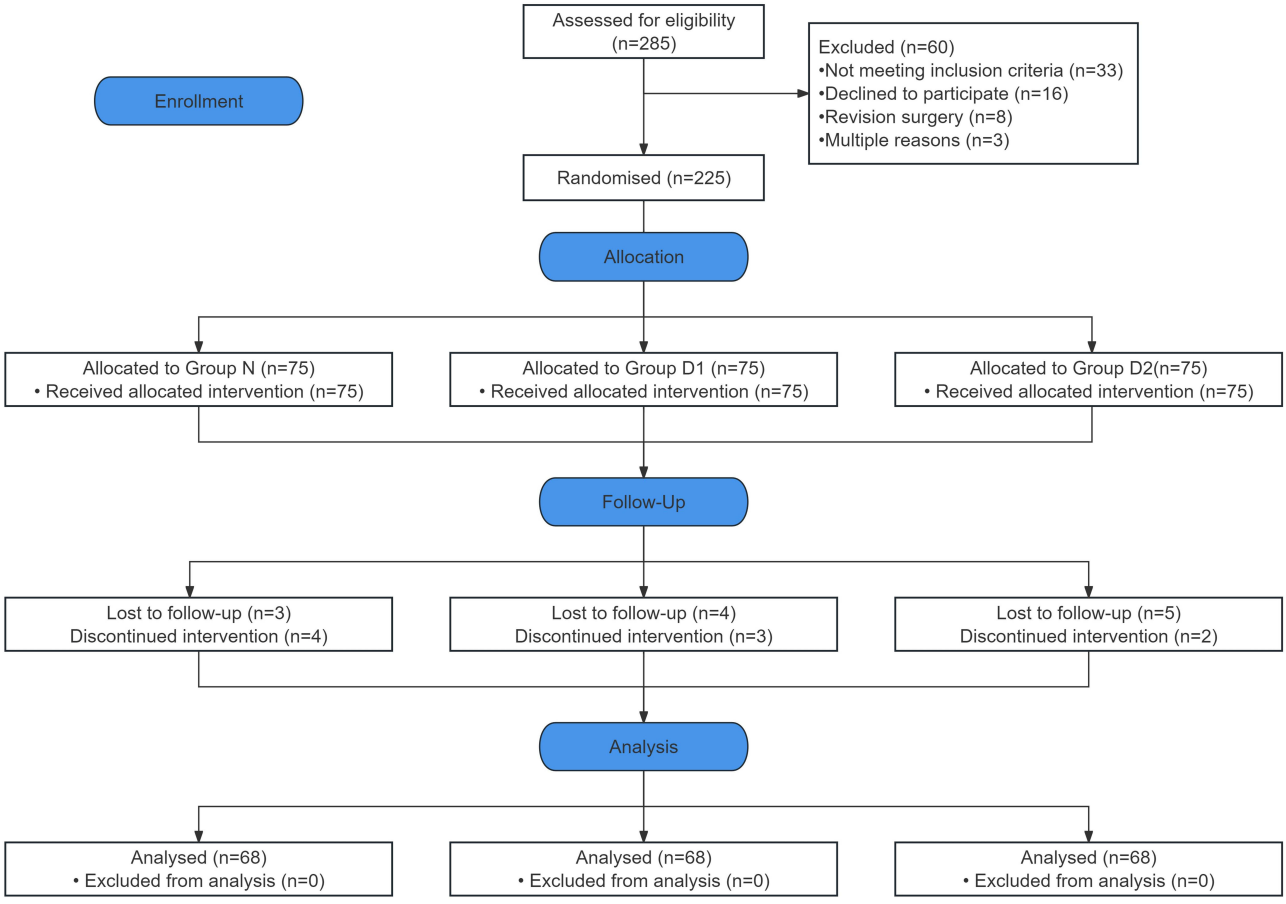

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

patients due to termination of intervention were removed from the trial. The remaining 204 patients were included in the data analysis (68 patients per group). After screening and eliminating EEG data by uniform criteria, EEG power spectral analysis was performed in 198 patients (64 in Group N, 67 in Group D1, and 67 in Group D2).

Demographic data were comparable among the three groups (Table 1). There were no differences in the duration of surgery and anesthesia, or the total volume administered. The propofol dosage was significantly reduced in Group D1 (414.2 ± 83.1 mg vs 456.6 ± 112.3 mg; $P = 0.013$) and Group D2 (396.8 ± 105.2 mg vs 456.6 ± 112.3 mg; $P = 0.001$) compared with Group N. The difference in tourniquet hypertension incidence was across groups (Group D2, 0 patient; Group D1, 5 patients [7.4%]; Group N, 16 patients [23.5%]; $P < 0.001$). However, no difference in intraoperative adverse events or length of stay was found among the three groups.

Primary Outcome

The median points in the global QoR-15 scores (Group N, 120 [116–123]; Group D1, 122 [118–126]; Group D2, 126 [123–129]; $P < 0.001$) as well as the scores of the three dimensions, including physical comfort (Group N, 43 [40–45]; Group

Table 1 Baseline Demographic and Clinical Characteristics

Characteristics	Group N (n=68)	Group D1 (n=68)	Group D2 (n=68)	*P*
Age (years)	69.0±6.5	69.1±6.0	68.7±5.6	0.892
Sex				0.302
Female	52 (76.5)	44 (64.7)	46 (67.6)	
Male	16 (23.5)	24 (35.3)	22 (32.4)	
BMI (kg/m^2)	25.9±2.8	25.8±2.8	25.0±2.6	0.084
History of anesthesia	21 (30.9)	22 (32.4)	31 (45.6)	0.145
ASA physical status				0.589
I	0	0	0	
II	31 (45.6)	34 (50.0)	37 (54.4)	
III	37 (54.4)	34 (50.0)	31 (45.6)	
History of diseases				
Hypertension	42 (61.8)	46 (67.6)	35 (51.5)	0.149
Diabetes mellitus	12 (17.6)	10 (14.7)	8 (11.8)	0.626
Coronary artery disease	3 (4.4)	11 (16.2)	6 (8.8)	0.066
TIA	8 (11.8)	11 (16.2)	6 (8.8)	0.421
Anesthesia maintenance				
Propofol (mg)	456.6±112.3	414.2±83.1	396.8±105.2	0.005
Sufentanil (μg)	15.0±5.5	13.1±5.0	13.4±4.8	0.070
Remifentanil (μg)	700.8±222.0	680.2±209.7	649.3±177.2	0.334
Femoral nerve block	68 (100)	68 (100)	68 (100)	1.000
Sciatic nerve block	68 (100)	68 (100)	68 (100)	1.000
Surgery time (min)	73.4±15.3	72.0±13.1	71.5±15.0	0.701
Anesthesia time (min)	101.7±16.3	100.4±16.5	96.7±17.5	0.193
Total volume (mL)	1166.2±227.0	1173.5±216.2	1181.0±293.8	0.941
Tourniquet hypertension	16 (23.5)	5 (7.4)	0	<0.001
Intraoperative adverse events				
Hypotension	9 (13.2)	11 (16.2)	10 (14.7)	0.899
Hypertension	16 (23.5)	11 (16.2)	9 (13.2)	0.268
Bradycardia	15 (22.1)	21 (30.9)	27 (39.7)	0.084
Extubation time (min)	10.7 ± 6.7	11.7 ± 5.3	14.4 ± 8.0	0.005
PACU duration (min)	35.8 ± 9.5	34.7 ± 8.4	37.4 ± 10.6	0.256
Total LOS (d)	8.8 ± 2.3	8.4 ± 2.1	8.5 ± 2.4	0.551

Note: Data are presented as number (%) or mean ± SD, as appropriate.
Abbreviations: BMI, Body Mass Index; ASA, American Society of Anesthesiologists; TIA, Transient ischemic attack; PACU, post-anesthesia care unit; LOS, length of stay.

https://doi.org/10.2147/DDDT.S536217

D1, 44 [41–47]; Group D2, 48 [44–50]; $P < 0.001$), pain (Group N, 17 [15–17]; Group D1, 17 [15–18]; Group D2, 17 [17–18]; $P = 0.002$), and emotional state (Group N, 37 [36–38]; Group D1, 38 [38–38]; Group D2, 38 [38–38]; $P < 0.001$) were significantly difference among the three groups on POD1 (Table 2). Post hoc analyses showed that there was a significant improvement in the QoR-15 scores of POD1 in Group D2 compared with Group N (median difference, 6 points [95% CI, 4 to 8 points]; $P < 0.001$) and Group D1 (median difference, 4 points [95% CI, 2 to 5 points]; $P = 0.001$), while the difference was not statistically significant between Group D1 and Group N (median difference, 3 points [95% CI, 1 to 5 points]; $P = 0.018$).

Secondary Outcomes

Preoperative EEG power spectrum analysis including the α and slow oscillation peak power were similar among the three groups (Figure S1 in supplementary material). As depicted in Figure 2, intraoperative power spectra analysis revealed that the slow oscillation peak power increased in Group D2 (4.2 ± 0.3 dB vs 3.4 ± 0.3 dB; $P = 0.001$) and Group D1 (4.0 ± 0.3 dB vs 3.4 ± 0.3 dB; $P = 0.005$) while the α oscillation peak power decreased in Group D2 (0.7 ± 0.1 dB vs 0.9 ± 0.1 dB; $P < 0.001$) and Group D1 (0.7 ± 0.1 dB vs 0.9 ± 0.1 dB; $P < 0.001$) compared with Group N. No significant difference was observed between

Table 2 Global and Dimensional 15-Item Quality of Recovery Scores

	Group N (n=68)	Group D1 (n=68)	Group D2 (n=68)	*P*	D1 vs N		D2 vs N		D1 vs D2	
					Median Difference (95% CI)	*P*	Median Difference (95% CI)	*P*	Median Difference (95% CI)	*P*
Global QoR-15 (points)										
Preoperative	141 (138, 143)	141 (138, 143)	141 (139, 143)	0.930						
POD1	120 (116, 123)	122 (118, 126)	126 (123, 129)	<0.001	3 (1, 5)	0.018	6 (4, 8)	<0.001	4 (2, 5)	0.001
POD3	135 (134, 138)	137 (134, 138)	137 (135, 138)	0.080						
5 dimensions										
Physical comfort (points)										
Preoperative	50 (47, 50)	50 (46, 50)	49 (47, 50)	0.731						
POD1	43 (40, 45)	44 (41, 47)	48 (44, 50)	<0.001	2 (0, 3)	0.026	4 (3, 6)	<0.001	3 (1, 4)	<0.001
POD3	49 (48, 50)	50 (47, 50)	50 (48, 50)	0.418						
Physical independence (points)										
Preoperative	20 (20, 20)	20 (20, 20)	20 (20, 20)	0.691						
POD1	4 (4,4)	4 (4,4)	4 (4,4)	1.000						
POD3	12 (10, 12)	12 (10, 12)	12 (10, 12)	0.160						
Psychological support (points)										
Preoperative	20 (20, 20)	20 (20, 20)	20 (20, 20)	1.000						
POD1	20 (20, 20)	20 (20, 20)	20 (20, 20)	0.368						
POD3	20 (20, 20)	20 (20, 20)	20 (20, 20)	1.000						
Pain (points)										
Preoperative	17 (15, 17)	17 (15, 17)	17 (17, 18)	0.053						
POD1	17 (15, 17)	17 (15, 18)	17 (17, 18)	0.002	0 (0, 1)	0.194	1 (0, 1)	0.001	1 (0, 1)	0.045
POD3	18 (17, 18)	18 (17, 18)	18 (18, 18)	0.131						
Emotional state (points)										
Preoperative	36 (35, 36)	36 (35, 36)	36 (35, 37)	0.915						
POD1	37 (36, 38)	38 (38, 38)	38 (38, 38)	<0.001	0 (0, 1)	<0.001	1 (0, 1)	<0.001	1 (0, 1)	0.112
POD3	38 (38, 38)	38 (38, 38)	38 (38, 38)	0.110						

Note: Data are presented as median (interquartile).
Abbreviations: QoR-15, 15-item Quality of Recovery; POD1, postoperative day 1; POD3, postoperative day 3.

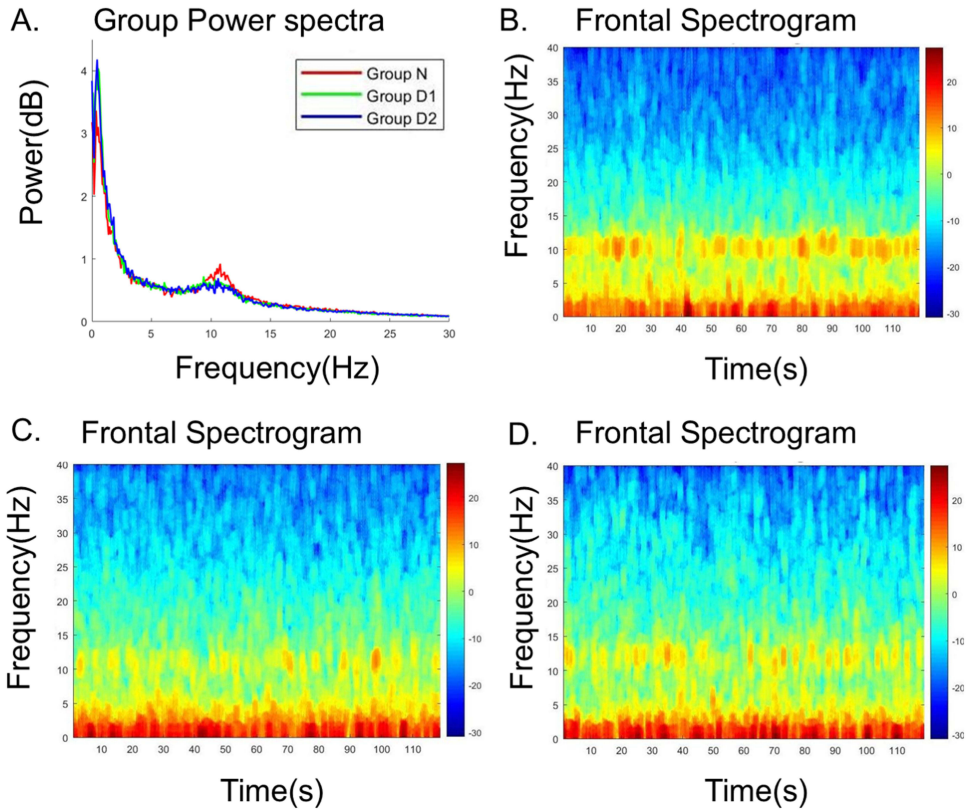

Figure 2 Intraoperative electroencephalogram (EEG) power spectra analysis. (**A**) Group power spectral comparing EEG power with frequency in patients in the saline group (Group (N) (red line), the 0.3 μg/kg/h dexmedetomidine group (Group D1) (green line) and the 0.6 μg/kg/h dexmedetomidine group (Group D2) (blue line). (**B**) Frontal spectrogram of representative patient treated with saline (Group N). (**C**) Frontal spectrogram of representative patient treated with 0.3 μg/kg/h dexmedetomidine (Group D1). (**D**) Frontal spectrogram of representative patient treated with 0.6 μg/kg/h dexmedetomidine (Group D2).

Group D1 and Group D2 in EEG power spectra. However, there were no difference in the α and slow oscillation peak power among the three groups during recovery period (Figure S2 in supplementary material). Consequently, the α and slow oscillation peak power in the preoperative, intraoperative, and recovery periods, respectively, were selected for correlation with the global QoR-15 scores on POD1 (Figure 3). Linear regression analysis revealed that the intraoperative slow oscillation peak power had weak positive correlations with the QoR-15 scores on POD1 ($r = 0.319$, $P < 0.001$).

No significant difference was observed in the global and dimensional QoR-15 scores on POD3 among the three groups. The utilization of flurbiprofen axetil on POD1 differed among the three groups (47 patients [69.1%] vs 42 patients [61.8%] vs 33 patients [48.5%]; $P = 0.046$), and no significant difference was observed in the consumption of other analgesics (Table S1 in supplementary material).

Furthermore, better hemodynamic status was observed in patients allocated to Group D1 and Group D2, compared with patients allocated to Group N (Figure 4). Intraoperative vasoactive drug use was presented in Table S2 in supplementary material. There was no significant difference among the three groups in the use of atropine and ephedrine. In terms of norepinephrine use, it was significantly lower in Group D1 (2 patients [2.9%] vs 12 patients [17.6%]; $P = 0.005$) and Group D2 (1 patients [1.5%] vs 12 patients [17.6%]; $P = 0.001$) compared to Group N.

Discussion

In this randomized clinical trial, elderly patients receiving 0.6 μg/kg/h dexmedetomidine had superior recovery on POD1, especially in the three dimensions of physical comfort, pain, and emotional state compared with patients receiving saline and 0.3 μg/kg/h dexmedetomidine. From the perspective of EEG power spectrum analysis, the application of dexmedetomidine at different doses increased the slow oscillation peak power, and correlation analyses showed a weak positive

https://doi.org/10.2147/DDDT.S536217

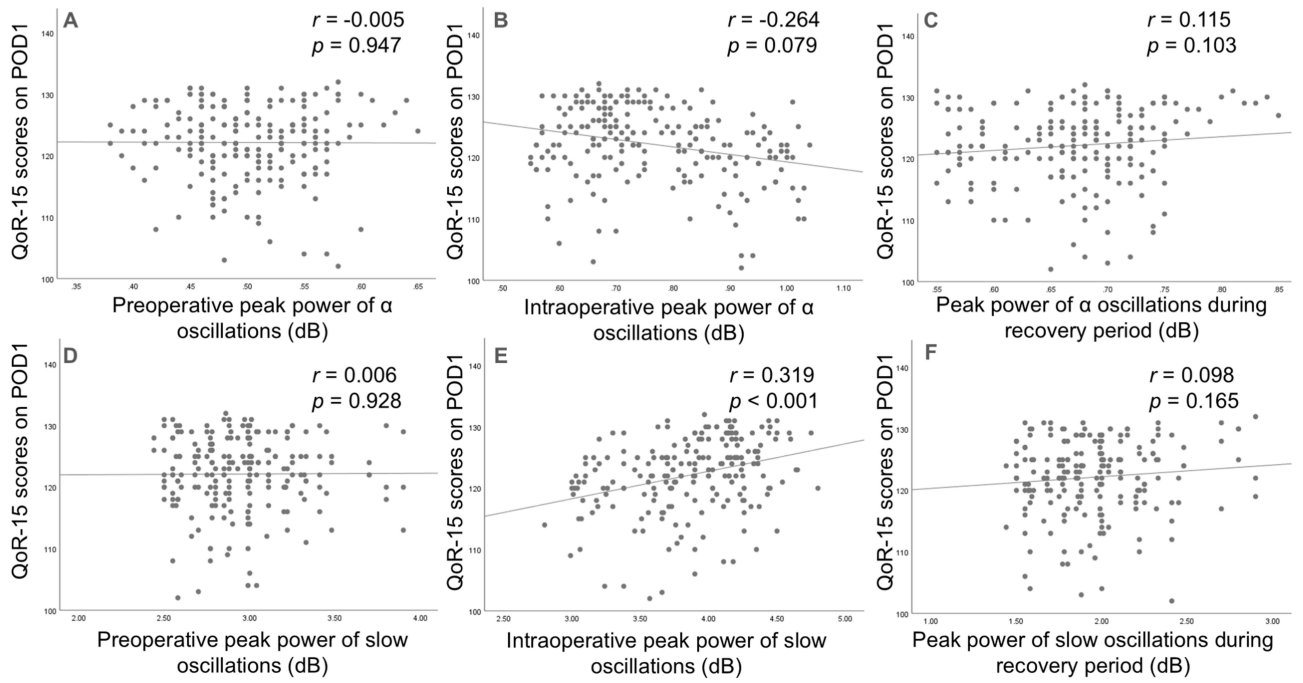

Figure 3 Correlation analysis of α and slow oscillation peak power with global Quality of Recovery-15 (QoR-15) scores on POD1.(**A**) The correlation between preoperative peak power of α oscillations and QoR - 15 scores on POD1. (**B**) The correlation of intraoperative peak power of α oscillations with QoR - 15 scores on POD1. (**C**) The correlation between peak power of α oscillations during the recovery period and QoR - 15 scores on POD1. (**D**) The correlation of preoperative peak power of slow oscillations and QoR - 15 scores on POD1. (**E**) The correlation between intraoperative peak power of slow oscillations and QoR - 15 scores on POD1. (**F**) The correlation of peak power of slow oscillations during the recovery period with QoR-15 scores on POD1.

correlation between intraoperative slow oscillation peak power and QoR-15 scores on POD1. In addition, dexmedetomidine infusion at 0.6 μg/kg/h also reduced the incidence of tourniquet hypertension.

The QoR-15 scale consists of 5 dimensions, and patients receiving 0.6 μg/kg/h dexmedetomidine in this study scored better in physical comfort, pain and emotional state on POD1. Due to the severe trauma caused by TKA, adverse consequences including pain and sleep disturbances remain important factors affecting postoperative recovery.[34,35] Grosu et al found that approximately 58% of TKA patients experienced moderate to severe pain on POD1.[34] Moreover, acute sleep disturbances after TKA can last for a long time.[35,36] Intraoperative application of dexmedetomidine was considered to mitigate postoperative pain by reducing inflammatory mediators and substance P induced by surgical trauma.[37,38] Furthermore, voltage-gated sodium channels in the dorsal horn have been shown to be critical in pain transmission.[39,40] These studies have also shown that dexmedetomidine inhibits sodium channels. This means that the drug can modulate pain and perception through the locus coeruleus and dorsal horn, while also affecting pain transmission and conduction, thereby broadening its analgesic efficacy. Dexmedetomidine at 0.6 μg/kg/h was also effective in improving the patient's sleep quality on POD1, consistent with previous reports indicating that a specific dose of dexmedetomidine may ameliorate postoperative sleep disturbances.[41,42] Then, better postoperative emotional state scores were attributed to satisfactory postoperative analgesia and improved sleep quality.[43,44]

Nevertheless, there were no differences on the physical independence and psychological support dimensions among the three groups on POD 1. In the early stage after TKA, especially within 24 hours, elderly patients commonly experience knee swelling, pain, muscle weakness, and limited mobility.[45] These physiological constraints significantly impede the expression of physical independence in the QoR-15 scale, leaving patients with relatively poor abilities in independent activities during this period. This widespread functional limitation may lead to scores of this dimension clustering at the lower end of the scale, resulting in a floor effect. Additionally, this study adopted single-center standardized perioperative management, where all patients received consistent care procedures and communication patterns, and all had access to family companionship and support. This may have diminished the discriminability of intergroup differences in the dimension of psychological support. Notably, dexmedetomidine had no effect on QoR-15

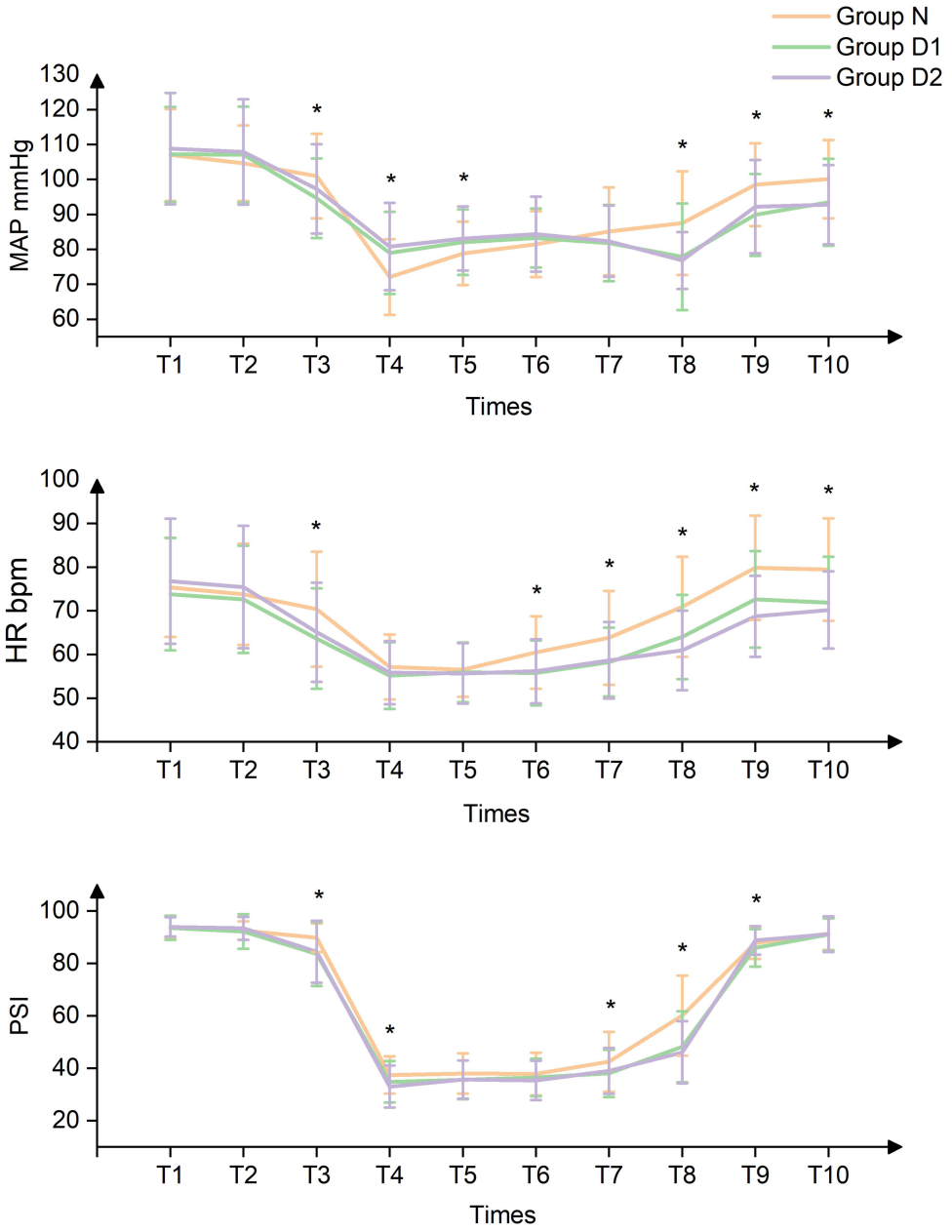

Figure 4 Perioperative hemodynamic variables. T1, entering the operating room; T2, loading dose of study drug at start of pumping; T3, loading dose of study drug at end of pumping; T4, establishing the airway; T5, at the start of surgery; T6, 30 min after the surgery; T7, 60 min after the surgery; T8, at the end of surgery; T9, after extubation; T10, leaving post-anesthesia care unit. *Indicates $P < 0.05$ within groups.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; PSI, patient state index.

scores on POD3. This finding might be related to the timing and dosage of dexmedetomidine used, the standardized postoperative care and well-established analgesic protocol after surgery.

Influenced by many factors such as patient age, surgical stimulation, drug concentration and physiological state,[46] the reliability of processing EEG-derived metrics (PSI) for depth of anesthesia monitoring is questionable. We therefore further analyzed the EEG waveforms of patients and found that the combination of dexmedetomidine and propofol elicited larger slow oscillations and increased the slow oscillation peak power. Meanwhile, correlation analysis showed a weak positive correlation between intraoperative slow oscillation peak power and QoR-15 scores on POD1. These results indicated that deepening anesthesia within an appropriate range could promote postoperative recovery to some extent. Studies have shown that slow oscillations during non-rapid eye movement sleep play a pivotal role in sleep

https://doi.org/10.2147/DDDT.S536217

homeostasis and higher cognitive function.[47,48] In addition, dexmedetomidine-induced modulation of slow-wave activity has been demonstrated to be an EEG marker of anesthesia-induced metabolic inhibition, which allows brain cells to take a full rest.[49] Accordingly, dexmedetomidine may be beneficial in restoring higher cognitive function and quality of life in elderly patients after surgery by deepening anesthesia and suppressing the stress response. However, the weak correlation between intraoperative slow oscillation peak power and QoR-15 scores on POD1 may be attributed to many factors affecting the quality of postoperative recovery, and the changes in brain electrical activity are only part of the mechanism by which dexmedetomidine improves postoperative QoR.

Notably, continuous infusion of low-dose dexmedetomidine (0.3 μg/kg/h) improved EEG parameters, such as slow oscillatory power, but did not significantly improve the quality of recovery after surgery compared with patients receiving normal saline. This may stem from the fact that EEG changes reflect only the neurophysiological effects of the drug, whereas clinical recovery results from a combination of factors such as inflammation, pain, and sleep. Low-dose dexmedetomidine may not provide sufficient anti-inflammatory or analgesic effects to translate changes in EEG waveforms into measurable improvements in QoR-15 scores, especially in elderly TKA patients with strong surgical stress.

It is worth mentioning that patients in the dexmedetomidine groups used significantly less propofol. To some extent, it means that continuous intravenous infusion of dexmedetomidine can induce deeper anesthesia in elderly patients undergoing general anesthesia, which is consistent with our previous findings that dexmedetomidine enhances the effect of propofol anesthesia by increasing the strength of slow wave oscillations.[18] This was also confirmed by the decrease in PSI. Although there was no significant difference in PSI among the three groups in this study, the average PSI in the saline group was still higher than that in the dexmedetomidine groups. This slight difference in the depth of anesthesia may affect the intraoperative slow wave oscillation power and α oscillation power, resulting in an increase in the peak slow wave oscillation power and a decrease in the peak α oscillation power in the dexmedetomidine groups. Future studies can focus on the effects of dexmedetomidine combined with propofol on more accurate changes in intraoperative slow wave oscillation power and alpha oscillation power under the same anesthesia depth and similar balance of cerebral oxygen supply and demand.

Dexmedetomidine inhibits sympathetic excitation, predisposing to hypotension and bradycardia. In addition, dexmedetomidine similarly activate peripheral α2-adrenergic receptors, leading to transient hypertension.[50,51] However, there was no significant difference in these adverse events among the three groups in our study. And the hemodynamic changes were more stable in patients who received dexmedetomidine compared to those who received saline. These results may stem from the relatively conservative dose of dexmedetomidine used in this study and the relatively strict exclusion criteria that excluded patients with severe bradycardia. Moreover, it has been shown that the anti-inflammatory properties of dexmedetomidine can reduce the release of proinflammatory cytokines such as IL-6 and TNF-α,[52] which is essential for preventing complications such as infection and delayed healing after joint replacement surgery. Considering the utilization of tourniquets during TKA and the positive effect of dexmedetomidine in reducing the stress response, we paid close attention to the incidence of intraoperative tourniquet hypertension. As expected, patients treated with dexmedetomidine during surgery had a significantly lower incidence of tourniquet hypertension compared to patients receiving saline. Moreover, all patients underwent well-established regional block techniques including femoral and sciatic nerve blocks preoperatively, which may have contributed to the lower incidence of tourniquet hypertension in the dexmedetomidine group in our study compared to previous studies.[30,53]

This study has several limitations. First, our study showed that dexmedetomidine at 0.6 μg/kg/h was superior to dexmedetomidine at 0.3 μg/kg/h and saline in improving the QoR on POD1; however, the optimal dose of dexmedetomidine needs to be further explored and investigated. Second, the lack of data on postoperative delirium remains a limitation of this study, despite the fact that our main observation was the quality of postoperative recovery. Finally, the study was conducted in a single center and was not representative of the wider population, limiting the generalizability of the findings.

Conclusions

This study demonstrated that intravenous infusion of a loading dose of dexmedetomidine (0.5 μg/kg) within 10 min before anesthesia induction, followed by a maintenance infusion of 0.6 μg/kg/h dexmedetomidine improved the QoR on POD 1 in elderly TKA patients compared with 0.3 μg/kg/h dexmedetomidine and saline. Furthermore, dexmedetomidine deepened the depth of anesthesia by increasing the slow oscillation peak power in the appropriate range, which partially correlated with improved QoR-15 scores on POD1. This study provides valuable anesthesia strategies for elderly patients

with TKA to improve the postoperative QoR. Future studies can verify the results across a wider patient sample and further explore how to improve postoperative recovery quality in elderly patients based on EEG changes.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author (Lijian Chen, email: chenlijian77@126.com) on reasonable request.

Ethics Approval

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (approval number: PJ2022-13-12). Written informed consent was obtained from all patients or their legal surrogates.

Acknowledgments

The authors give special thanks to the Department of Joint Surgery and nursing teams of the First Affiliated Hospital of Anhui Medical University.

Funding

This study was supported by Beijing Health Alliance Charitable Foundation (S251 to Lijian Chen), Outstanding Scientific Research and Innovation Team Program for Universities in Anhui Province (2024AH010015 to Lijian Chen) and Foundation Project of Anhui Medical University (grant number 2022xkj169 to Lei Zhang) which provided funds for collection and analysis of clinical data.

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet*. 2018;392(10158):1672–1682. doi:10.1016/S0140-6736(18)32344-4
2. Wu CL, Rowlingson AJ, Partin AW, et al. Correlation of postoperative pain to quality of recovery in the immediate postoperative period. *Reg Anesth Pain Med*. 2005;30(6):516–522. doi:10.1097/00115550-200511000-00003
3. Kovoor JG, Stretton B, Kerr LD, et al. Sleep and postoperative recovery: waking up to the evidence. *ANZ J Surg*. 2022;92(5):953–954. doi:10.1111/ans.17422
4. Chan SP, Ip KY, Irwin MG. Peri-operative optimisation of elderly and frail patients: a narrative review. *Anaesthesia*. 2019;74 Suppl 1:80–89.
5. Paris A, Tonner PH. Dexmedetomidine in anaesthesia. *Curr Opin Anaesthesiol*. 2005;18(4):412–418. doi:10.1097/01.aco.0000174958.05383.d5
6. Deiner S, Luo X, Lin HM, et al. Intraoperative infusion of dexmedetomidine for prevention of postoperative delirium and cognitive dysfunction in elderly patients undergoing major elective noncardiac surgery: a randomized clinical trial. *JAMA Surg*. 2017;152(8):e171505. doi:10.1001/jamasurg.2017.1505
7. Shariffuddin II, Teoh WH, Wahab S, Wang CY. Effect of single-dose dexmedetomidine on postoperative recovery after ambulatory ureteroscopy and ureteric stenting: a double blind randomized controlled study. *BMC Anesthesiol*. 2018;18(1):3. doi:10.1186/s12871-017-0464-6
8. Long K, Ruiz J, Kee S, et al. Effect of adjunctive dexmedetomidine on postoperative intravenous opioid administration in patients undergoing thyroidectomy in an ambulatory setting. *J Clin Anesth*. 2016;35:361–364. doi:10.1016/j.jclinane.2016.08.036
9. Akeju O, Hobbs LE, Gao L, et al. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: a pilot study. *Clin Neurophysiol*. 2018;129(1):69–78. doi:10.1016/j.clinph.2017.10.005
10. Colin PJ, Hannivoort LN, Eleveld DJ, et al. Dexmedetomidine pharmacokineticpharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation. *Brit J Anaesth*. 2017;119(2):200–210. doi:10.1093/bja/aex085
11. Bekker A, Haile M, Kline R, et al. The effect of intraoperative infusion of dexmedetomidine on the quality of recovery after major spinal surgery. *J Neurosurg Anesthesiol*. 2013;25(1):16–24. doi:10.1097/ANA.0b013e31826318af
12. Kim SY, Kim JM, Lee JH, Song BM, Koo BN. Efficacy of intraoperative dexmedetomidine infusion on emergence agitation and quality of recovery after nasal surgery. *Br J Anaesth*. 2013;111(2):222–228. doi:10.1093/bja/aet056
13. Kim SH, Oh YJ, Park BW, Sim J, Choi YS. Effects of single-dose dexmedetomidine on the quality of recovery after modified radical mastectomy: a randomised controlled trial. *Minerva Anestesiol*. 2013;79(11):1248–1258.
14. Sherif AA, Elsersy HE. The impact of dexmedetomidine or xylocaine continuous infusion on opioid consumption and recovery after laparoscopic sleeve gastrectomy. *Minerva Anestesiol*. 2017;83(12):1274–1282. doi:10.23736/S0375-9393.17.11855-9
15. Hakim KYK, Wahba WZB. Opioid-free total intravenous anesthesia improves postoperative quality of recovery after ambulatory gynecologic laparoscopy. *Anesth Essays Res*. 2019;13(2):199–203. doi:10.4103/aer.AER_74_19
16. Akeju O, Pavone KJ, Westover MB, et al. A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. *Anesthesiology*. 2014;121(5):978–989. doi:10.1097/ALN.0000000000000419

17. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists. *Anesthesiology*. 2015;123(4):937–960. doi:10.1097/ALN.0000000000000841
18. Zhang L, Fang K, Tao S, et al. Electroencephalography-demonstrated mechanisms of dexmedetomidine-mediated deepening of propofol anesthesia: an observational study. *Perioper Med*. 2021;10(1):44. doi:10.1186/s13741-021-00213-4
19. Zhang L, Li H, Deng LY, et al. Electroencephalogram mechanism of dexmedetomidine deepening sevoflurane anesthesia. *Front Neurosci-Switz*. 2022;16:913402.
20. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332. doi:10.1136/bmj.c332
21. Purdon PL, Pavone KJ, Akeju O, et al. The ageing brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. *Br J Anaesth*. 2015;115 Suppl 1(Suppl 1):i46–i57. doi:10.1093/bja/aev213
22. Li CJ, Wang BJ, Mu DL, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. *Brit J Surg*. 2020;107(2):e123–e32. doi:10.1002/bjs.11354
23. Eskandr AM, Metwally AA, Ahmed AA, et al. Dexmedetomidine as a part of general anaesthesia for caesarean delivery in patients with pre-eclampsia: a randomised double-blinded trial. *Eur J Anaesthesiol*. 2018;35(5):372–378. doi:10.1097/EJA.0000000000000776
24. Marty P, Chassery C, Rontes O, et al. Combined proximal or distal nerve blocks for postoperative analgesia after total knee arthroplasty: a randomised controlled trial. *Br J Anaesth*. 2022;129(3):427–434. doi:10.1016/j.bja.2022.05.024
25. Lavand'homme PM, Kehlet H, Rawal N, Joshi GP. Pain management after total knee arthroplasty: Procedure specific postoperative pain management recommendations. *Eur J Anaesthesiol*. 2022;39(9):743–757. doi:10.1097/EJA.0000000000001691
26. Kopp SL, Børglum J, Buvanendran A, et al. Anesthesia and analgesia practice pathway options for total knee arthroplasty: an evidence-based review by the American and European societies of regional anesthesia and pain medicine. *Reg Anesth Pain Med*. 2017;42(6):683–697.
27. Sah AP, Liang K, Sclafani JA. Optimal multimodal analgesia treatment recommendations for total joint arthroplasty: a critical analysis review. *JBJS Rev*. 2018;6(6):e7. doi:10.2106/JBJS.RVW.17.00137
28. Bu XS, Zhang J, Zuo YX. Validation of the Chinese version of the quality of recovery-15 score and its comparison with the post-operative quality recovery scale. *Patient*. 2016;9(3):251–259. doi:10.1007/s40271-015-0148-6
29. Wahal C, Grant SA, Gadsden J, Rambhia MT, Bullock WM. Femoral artery block (FAB) attenuates thigh tourniquet-induced hypertension: a prospective randomized, double-blind, placebo-controlled trial. *Reg Anesth Pain Med*. 2021;46(3):228–232. doi:10.1136/rapm-2020-102113
30. Xu F, Wang X, Li Y, et al. Combined femoral artery block and femoral nerve block reduces thigh tourniquet-induced hypertension. *J Clin Anesth*. 2023;85:111039. doi:10.1016/j.jclinane.2022.111039
31. Myles PS, Myles DB. An updated minimal clinically important difference for the QoR-15 scale. *Anesthesiology*. 2021;135(5):934–935. doi:10.1097/ALN.0000000000003977
32. Gasbjerg KS, Hagi-Pedersen D, Lunn TH, et al. Effect of dexamethasone as an analgesic adjuvant to multimodal pain treatment after total knee arthroplasty: randomised clinical trial. *BMJ*. 2022;376:e067325. doi:10.1136/bmj-2021-067325
33. Bokil H, Andrews P, Kulkarni JE, Mehta S, Mitra PP. Chronux: a platform for analyzing neural signals. *J Neurosci Meth*. 2010;192(1):146–151. doi:10.1016/j.jneumeth.2010.06.020
34. Grosu I, P L, Thienpont E. Pain after knee arthroplasty: an unresolved issue. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(8):1744–1758. doi:10.1007/s00167-013-2750-2
35. Manning BT, Kearns SM, Bohl DD, et al. Prospective assessment of sleep quality before and after primary total joint replacement. *Orthopedics*. 2017;40(4):E636–E40. doi:10.3928/01477447-20170411-01
36. Chen AF, Orozco FR, Austin LS, et al. Prospective evaluation of sleep disturbances after total knee arthroplasty. *J Arthroplasty*. 2016;31(1):330–332. doi:10.1016/j.arth.2015.07.044
37. Cheung CW, Qiu Q, Ying AC, et al. The effects of intra-operative dexmedetomidine on postoperative pain, side-effects and recovery in colorectal surgery. *Anaesthesia*. 2014;69(11):1214–1221. doi:10.1111/anae.12759
38. Weerink MAS, Struys M, Hannivoort LN, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. *Clin Pharmacokinet*. 2017;56(8):893–913. doi:10.1007/s40262-017-0507-7
39. Im ST, Jo YY, Han G, et al. Dexmedetomidine inhibits voltage-gated sodium channels via α 2-adrenoceptors in trigeminal ganglion neurons. *Mediators Inflamm*. 2018;2018:1782719. doi:10.1155/2018/1782719
40. Maruta T, Nemoto T, Satoh S, et al. Dexmedetomidine and clonidine inhibit the function of Na(v)1.7 independent of α(2)-adrenoceptor in adrenal chromaffin cells. *J Anesth*. 2011;25(4):549–557. doi:10.1007/s00540-011-1168-6
41. Chen Z, Tang R, Zhang R, Jiang Y, Liu Y. Effects of dexmedetomidine administered for postoperative analgesia on sleep quality in patients undergoing abdominal hysterectomy. *J Clin Anesth*. 2017;36:118–122. doi:10.1016/j.jclinane.2016.10.022
42. Duan G, Wang K, Peng T, Wu Z, Li H. The effects of intraoperative dexmedetomidine use and its different dose on postoperative sleep disturbance in patients who have undergone non-cardiac major surgery: a real-world cohort study. *Nat Sci Sleep*. 2020;12:209–219. doi:10.2147/NSS.S239706
43. Horn-Hofmann C, Scheel J, Dimova V, et al. Prediction of persistent post-operative pain: Pain-specific psychological variables compared with acute post-operative pain and general psychological variables. *Eur J Pain*. 2018;22(1):191–202. doi:10.1002/ejp.1115
44. Gerbershagen HJ, Aduckathil S, van Wijck AJ, et al. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology*. 2013;118(4):934–944. doi:10.1097/ALN.0b013e31828866b3
45. Wang Q, Jin Q, Cai L, et al. Efficacy of diosmin in reducing lower-extremity swelling and pain after total knee arthroplasty: a randomized, controlled multicenter trial. *J Bone Joint Surg Am*. 2024;106(6):492–500. doi:10.2106/JBJS.23.00854
46. Bombardieri AM, Wildes TS, Stevens T, et al. Practical training of anesthesia clinicians in electroencephalogram-based determination of hypnotic depth of general anesthesia. *Anesth Anal*. 2020;130(3):777–786. doi:10.1213/ANE.0000000000004537
47. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull*. 2003;62(2):143–150. doi:10.1016/j.brainresbull.2003.09.004
48. Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. *Nature*. 2006;444(7119):610–613. doi:10.1038/nature05278
49. Ikeda T, Amorim E, Miyazaki Y, et al. Post-cardiac arrest sedation promotes electroencephalographic slow-wave activity and improves survival in a mouse model of cardiac arrest. *Anesthesiology*. 2022;137(6):716–732. doi:10.1097/ALN.0000000000004390

50. Almeida AN, Tavares C, Tibano A, et al. Dexmedetomidine for awake craniotomy without laryngeal mask. *Arquivos de Neuro-Psiquiatria*. 2005;63 (3b):748–750. doi:10.1590/S0004-282X2005000500005
51. Ibacache ME, Muñoz HR, Brandes V, Morales AL. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. *Anesth Analg*. 2004;98(1):60–63. doi:10.1213/01.ANE.0000094947.20838.8E
52. Moldovan F. Role of serum biomarkers in differentiating periprosthetic joint infections from aseptic failures after total hip arthroplasties. *J Clin Med*. 2024;13(19):5716. doi:10.3390/jcm13195716
53. Abdallah FW, Chan VW, Gandhi R, et al. The analgesic effects of proximal, distal, or no sciatic nerve block on posterior knee pain after total knee arthroplasty: a double-blind placebo-controlled randomized trial. *Anesthesiology*. 2014;121(6):1302–1310. doi:10.1097/ALN.0000000000000406