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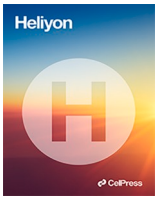

Research article

The feasibility of dexmedetomidine-led anesthesia maintenance strategy during major abdominal surgery

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ABSTRACT

Background: Dexmedetomidine is known for its selective action on α2-adrenoceptor sites and is recognized for its neuroprotective capabilities. It can improve postoperative cognitive function. Commonly used anesthetics, such as sevoflurane and propofol, have been reported to affect postoperative cognitive function. Therefore, it could be valuable to explore dexmedetomidine-led anesthesia strategy. This study was designed to assess the performance, safety, and effective infusion rate in anesthesia maintenance, to explore a feasible dexmedetomidine-led anesthesia maintenance protocol, and to provide a foundation for potential combined anesthesia.

Methods: Thirty patients aged 18–60 years, classified as ASA I or II, undergoing abdominal surgery were involved. The anesthesia maintenance was achieved with dexmedetomidine, remifentanil and rocuronium. Dixon up-and-down sequential methodology was utilized to ascertain the ED50 of dexmedetomidine for maintaining Patient State Index (PSI) 25–40 (depth of stage III anesthesia). Intraoperative HR, BP and depth of anesthesia were monitored and controlled. The wake-up time from anesthesia, the incidence of intraoperative awareness and postoperative delirium, and the patients' satisfaction were assessed.

Results: The results indicated that dexmedetomidine-led anesthesia could maintain the depth of stage III anesthesia during abdominal surgery. The ED50 and ED95 of dexmedetomidine infusion rates during anesthesia maintenance were 2.298 μg/kg·h (95%CI: 2.190–2.404 μg/kg·h) and 3.765 μg/kg·h (95%CI: 3.550–4.050 μg/kg·h). Continuous infusion of dexmedetomidine and 0.1–0.3 μg/kg·min remifentanil could maintain PSI 25–40, and provide appropriate anesthesia depth for abdominal surgery. Perioperative bradycardia and hypertension could be rapidly corrected with atropine and nitroglycerin. The median wake-up time after anesthesia was 4.8 min, the perioperative maximum HR had significant correlation with wake-up time and intraoperative dexmedetomidine dose. No intraoperative awareness and postoperative delirium occurred; the patients were satisfied with dexmedetomidine-led anesthesia.

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Conclusions: dexmedetomidine-led strategy could maintain stable depth of anesthesia throughout surgery, and the ED50 of dexmedetomidine infusion rates was 2.298 μg/kg·h. Intraoperative HR, BP and depth of anesthesia require monitoring, the bradycardia and hypertension could be rapidly corrected.

1. Introduction

Dexmedetomidine, renowned for its high affinity to α2-adrenergic receptors, is endowed with sedative, analgesic, sympatholytic, and anxiolytic effects, rendering it an safe and potent agent for anesthesia in the perioperative milieu [1,2]. It exhibits neuroprotective effects by attenuating inflammation, mitigating cell apoptosis and autophagy, safeguarding the blood-brain barrier, and fortifying cellular structure [3–5]. Dexmedetomidine has been associated with a diminished occurrence of post-surgical confusion and an enhancement in cognitive recovery post non-cardiac procedures in the geriatric population [6]. Commonly used anesthetics, such as sevoflurane and propofol, have been reported to induce neurogenesis alteration and apoptosis, reduce proliferation of neural stem cells [7,8], and affect postoperative cognitive function. Our study showed that dexmedetomidine-led induction strategy could achieve the depth of stage III (surgical stage) anesthesia [9]. Therefore, dexmedetomidine-led strategy could also be feasible in anesthesia maintenance and provide advantages in cognitive function protection and postoperative recovery, especially for elderly or critically ill patients with cognitive impairment.

Although dexmedetomidine-led anesthesia has advantages, there are still issues need to be considered and explored. Firstly, dexmedetomidine does not directly affect myocardial contractility, but causes a dose-dependent decrease in heart rate (HR) and variations in blood pressure (BP) [10,11]. Therefore, the effect of dexmedetomidine-led maintenance strategy (with high dexmedetomidine infusion rate) on HR and BP needs to be explored. Secondly, low-dose dexmedetomidine induces a distinctive sedative response and has been described as "awake sedation", which exhibits sleep-like sedation properties and allows for prompt awakening upon stimulation [12]. Therefore, the characteristics of high-dose dexmedetomidine also needs to be explored. Diligent monitoring and precise control of anesthetic depth are necessary during the process [13]. Thirdly, the distribution half-life (t1/2α) of dexmedetomidine is 6 min, and elimination half-life (t1/2β) is approximately 2 h, and the duration of continuous infusion half-life (t1/2CS) extends with increasing infusion time. There was a potential for rebound excitation and withdrawal symptoms after long term dexmedetomidine infusion [14], so the safety of patients after dexmedetomidine anesthesia needs to be observed.

This study aimed to investigate a feasible dexmedetomidine-led anesthesia maintenance strategy, and to determine the effective infusion rate of dexmedetomidine to maintain stage III anesthesia, the impact of high dexmedetomidine infusion rates on perioperative HR and BP, and the wake-up time following dexmedetomidine-led anesthesia. Additionally, the study assessed patient satisfaction, intraoperative awareness, and postoperative delirium in dexmedetomidine-led anesthesia, and examined the relationships among perioperative HR, dexmedetomidine dosage and wake-up time. These insights offer an anesthesia protocol with potential advantages for both healthy and elderly patient populations and establish the groundwork for the formulation and application of future combined anesthesia strategies.

2. Materials & methods

Ethical approval

This study obtained approval from the Institutional Review Board (IRB) of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (No. 21/024–2695) and registered the study at Chinese Clinical Trial Registry (No. ChiCTR2200058005). Prior to the commencement of the study, written informed consent was secured from all individuals participating in the trial.

2.1. Study design

The study was conducted between August and November 2022. 34 patients aged 18–60 years, ASA I or II, undergoing abdominal surgery for gastric, colorectal and gynecologic tumors, were recruited. Patients with following criteria were excluded: BMI <18.5 or >30 kg/m2; sinus bradycardia (HR < 50 bpm); severe heart block, cardiac insufficiency (LVEF <50%); systemic or important organ infection; severe anemia; severe liver; renal; or thyroid dysfunction, neurological disease or use of central nervous system drugs; preoperative cognitive dysfunction (MMSE <24); long-term use of α adrenergic receptor blocking drugs, or allergy to the anesthetic drugs used in the study. Patient characteristics, including age, sex, body weight, height, temperature, ALT, AST, creatinine, urea, Hgb levels, MMSE scores, personal history, ASA grade and comorbidities, were recorded prior to surgery.

2.2. Anesthetic procedure

For the preoperative period, no patients received premedication. Monitoring devices such as electrocardiographs, pulse oximeters, and blood pressure gauges were utilized. Additionally, SedLine EEG sensors (SedLine Sedation Monitor, Masimo Co., USA), were employed for the assessment of the Patient State Index (PSI). PSI scores 50–100 indicate light sedation or being awake; 25–50 indicate

stage III anesthesia (surgical anesthesia); and 0–25 indicate deep sedation [15]. During anesthesia induction, 6 L/min oxygen was provided with facemasks. Anesthesia induction was started with intravenous 3 μg/kg sufentanil. 30 s later, dexmedetomidine (Yangtze River Pharmaceutical Group Co. Ltd, Jiangsu, China) and remifentanil were continuous infused (Silugao CP-730 TCI pump, Silugao Med Tech, Beijing, China), this dexmedetomidine-led anesthesia induction has been described in our study [9]. After sufficient depth of anesthesia was achieved (Observer's Assessment of Alertness/Sedation Scale = 1, Supplementary Table 1), 0.8 mg/kg rocuronium was infused, intubation was performed. For maintaining anesthesia, a continuous administration of dexmedetomidine and remifentanil was implemented, alongside a dosage range of 0.3–0.6 mg/kg·h for rocuronium.

For dexmedetomidine-led anesthesia maintenance, the initial administration velocity of dexmedetomidine for first patient was 1.5 μg/kg·h based on preliminary study. In order to keep patients at appropriate depth of anesthesia, PSI was evaluated every 10 min during maintenance. Previous study indicated that Bispectral Index was relatively lower when using dexmedetomidine compared to propofol for equivalent sedation level [16]. Based on these results and the preliminary experiment, the intraoperative PSI was maintained within the range of·25–40, lower than the recommended criteria for stage III anesthesia criteria (PSI 25–50). If PSI <25, the dexmedetomidine infusion rate was reduced by 0.3 μg/kg·h. Guided by initial experimental findings, the baseline administration velocity for dexmedetomidine was established at 0.9 μg/kg·h. With this rate, patients woke up soon after the infusion was discontinued. Further reduction of administration velocity could increase the risk of intraoperative awareness and are unnecessary. If PSI >40, the dexmedetomidine administration velocity was increased by 0.3 μg/kg·h. At any time, if PSI >45, 0.3ug/kg dexmedetomidine was infused, and the dexmedetomidine administration velocity increased by 0.3 μg/kg·h (Table 1). Based on preliminary experiment, 0–50 min after intubation was the adjustment period for infusion rate from initial rate to appropriate maintenance rate. Thus, 60–100 min after intubation was treated as the stable maintenance period for dexmedetomidine infusion and anesthesia. The average value during the period was calculated and considered as the maintenance infusion rate for stage III general anesthesia. Maintenance infusion rate was compared with initial rate. If maintenance administration velocity was less than or equal to the initial rate, initial administration velocity of next patient decreased by 0.3 μg/kg·h. If maintenance administration velocity was greater than initial rate, the initial administration velocity of next patient increased by 0.3 μg/kg·h. Patient recruitment was continued until there were at least six crossover pairs and at least 30 patients were completed. Crossover pair was defined as: maintenance infusion rate less (greater) than initial rate in one patient, and maintenance infusion rate greater (less) than initial rate in next one.

During dexmedetomidine-led anesthesia maintenance, intraoperative remifentanil infusion was to reduce surgical pain and related BP variation. The commencement rate for remifentanil administration was established at 0.2 μg/kg·min. When systolic blood pressure (SBP) dropped below 90 mmHg, the medication's infusion rate was decreased to 0.1 μg/kg·min. Conversely, for SBP exceeding 160 mmHg, the rate was raised to 0.3 μg/kg·min, and at SBP above 180 mmHg, 100 μg of nitroglycerine was administered. The infusion rate reverted to 0.2 μg/kg·min once BP normalized. In cases of bradycardia (heart rate below 45 bpm), 0.5 mg of atropine was given, and for persistent tachycardia (heart rate over 100 bpm), 10 mg of esmolol was administered (Table 1). When PSI was evaluated every 10 min, HR and BP were concurrently recorded.

During wake-up stage of dexmedetomidine-led anesthesia, the patients' conditions were closely monitored and recorded. At the end of surgeries, dexmedetomidine and remifentanil infusion was stopped. To counteract the neuromuscular blockade, a 2 mg/kg dose of sugammadex was administered. Extubation of the trachea was carried out once patients could open their eyes in response to verbal cues and had regained sufficient tidal volume and respiratory rate. The wake-up time (the time from stopping infusion of dexmedetomidine and remifentanil to patients' opening eyes) was recorded. Then the patients were transferred to Post-Anesthesia Care Unit (PACU), and oxygen was administered. HR, BP, SpO2 and postoperative complications were monitored and recorded. When the patients were fully awake, they were transferred to the ward, HR and BP were monitored and recorded. During postoperative period, if bradycardia (HR < 45 bpm) occurred, 0.5 mg atropine was given. On the 1st postoperative day, modified Brice interview (Supplementary Table 2) [17] was used to evaluate the occurrence of intraoperative awareness, Short Confusion Assessment Method (CAM-S, Supplementary Table 3) was used to evaluate the occurrence of postoperative delirium, and Iowa Satisfaction with Anesthesia Scale's (ISAS, Supplementary Table 4) was used to assess the patients' satisfaction with anesthesia.

2.3. Statistical analysis

The Dixon up-and-down sequential allocation method was utilized in this investigation, a recognized approach in anesthesiology for establishing the effective dosage (ED) of pharmacological agents [18]. Depends on the method, this study required at least 6 crossover points and 30 patients for statistical analysis.

Table 1
Intraoperative DEX and remifentanil adjustment measures.

Indicators	Measures	Interval
PSI <25	DEX infusion rate reduced 0.3 μg/kg·h, Minimum rate: 0.9 μg/kg·h	10 min
PSI >40	DEX infusion rate increased 0.3 μg/kg·h	10 min
PSI >45	0.3ug/kg DEX bolus infusion + DEX infusion rate increased 0.3 μg/kg·h	Continuous
SBP >160 mmHg	Remifentanil infusion rate increased to 0.3 μg/kg·min	10 min
SBP >180 mmHg	Remifentanil infusion rate increased to 0.3 μg/kg·min +100 μg nitroglycerine bolus infusion	10 min
SBP <90 mmHg	Remifentanil infusion rate reduced to 0.1 μg/kg·min	10 min

The statistical analyses were performed with GraphPad Prism 7.0 (GraphPad Software, San Diego, USA). Dose-response data of dexmedetomidine were analyzed by Probit regression. The dose-response relationship of dexmedetomidine was evaluated using Probit regression analysis, which involved constructing a dose-response curve with dose values on the X-axis and the percentage of responders on the Y-axis. The effective doses of dexmedetomidine for achieving Stage III anesthesia were derived from the linear interpolation of the Probit regression plot, expressed as the mean and 95% confidence interval. Both the ED50 and ED95 values were determined from this analysis, with the ED50 also calculated as the average from independent crossovers of the initial infusion rate.

The data with normal distribution, such as age, height, weight, HR, MAP, etc., were analyzed using the independent samples Student's t-test, with results reported as mean ± SD, other data were analyzed using the Kruskal-Wallis test and the results were presented as median (25th percentile, 75th percentile). Enumeration data were expressed as number (percentage). One-way ANOVA was used for perioperative HR, mean arterial pressure (MAP), and PSI comparison. $p < 0.05$ indicated a statistically significant difference. The sequential graph was created using Microsoft Excel software.

3. Results

The flow of participants in the investigation is detailed in Fig. 1. Of thirty-four individuals evaluated for suitability, two failed to satisfy the inclusion parameters and were subsequently omitted. In addition, surgery deferments resulted in the non-participation of two otherwise eligible individuals. Consequently, 30 participants were enrolled and successfully completed the study. The patients' characteristics before surgery were collected (Table 2), revealing an average age of 49.5 years and BMI of 23.7. Preoperative hepatic and renal functions were within normal range. MMSE scores were greater than 24, indicating intact preoperative cognitive function. Among the preoperative conditions, hypertension was noted in 8 patients, diabetes in 4, allergic rhinitis in 2, and one case of emphysema. Additionally, 7 participants had a smoking history, and 5 reported alcohol consumption. All patients underwent major abdominal tumor surgery, including 8 gastric surgeries, 15 colorectal surgeries, and 7 gynecologic surgeries.

Patients' characteristics during dexmedetomidine-led anesthesia induction and maintenance are recorded (Table 3). The induction dose of dexmedetomidine was 3.1 (3, 3.4) μg/kg, which was consistent with our previous study [9]. The duration of surgery was 3.1 ±

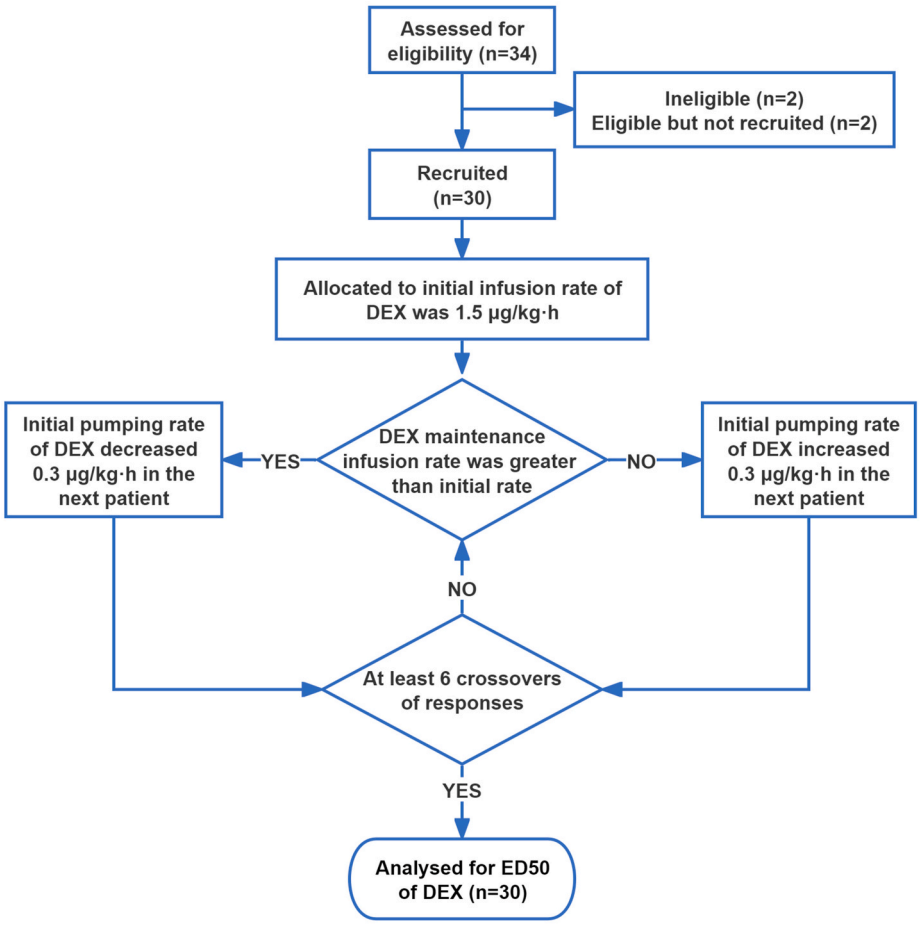


Fig. 1. Flow chart for this Dixon up-and-down sequential study.

Table 2
Subject characteristics. Data are presented as mean ± SD, median (interquartile range), or number (percentage).

Sex (Male/Female)	15/15
Age (year)	49.5 ± 6.7
Weight (kg)	66.9 ± 10.0
Height (cm)	167.9 ± 8.3
BMI (kg/m2)	23.7 ± 2.7
ALT (U/L)	14.2 (11.6, 21.8)
AST (U/L)	19.7 (16.7, 24.4)
Creatinine (μmol/L)	55.6 (55.6, 77.7)
Urea nitrogen (mmol/L)	4.6 ± 1.3
MMSE	29 (28, 30)
Smoking (%)	7 (23.3%)
Drinking (%)	5 (16.7%)
ASA grade (I/II)	19/11
Comorbidities	
Hypertension	8 (23.3%)
Diabetes	4 (13.3%)
Allergic rhinitis	2 (6.7%)
Emphysema	1 (3.3%)
Types of surgery	
Gastric surgery	8 (26.7%)
Colorectal surgery	15 (50.0%)
Gynecologic surgery	7 (23.3%)

0.7 h and the duration of anesthesia was 3.6 ± 0.7 h dexmedetomidine, remifentanil and rocuronium were used for anesthesia maintenance, and their doses during anesthesia (include induction and maintenance) were 3.23 ± 0.76 μg/kg·h, 12.99 ± 2.79 μg/kg·h and 0.44 ± 0.08 mg/kg·h respectively. Considered the effect of remifentanil on BP, we compared the intraoperative remifentanil infusion rates for hypertensive and non-hypertensive patients (13.33 ± 2.93 μg/kg·h and 12.86 ± 2.72 μg/kg·h), and there was no significant difference ($p = 0.518$). With verbal command, the patients regain their consciousness, and the PSI on that time point was 59.6 ± 6.4. PSI on leaving the operating room was 87.8 ± 5.4. No postoperative agitation, $SpO_2 < 90\%$, nausea and vomiting were observed. Postoperative shivering occurred in one patient.

The initial dexmedetomidine rates of the patients are shown in Fig. 2A. There were 12 crossovers according to Dixon up and down method, and the mean rate of 12 initial infusion rates of crossover pairs was 2.05 μg/kg·h. The responder data for each dosage level was utilized to construct a sigmoidal dose-response curve, which visually represents the relationship between the dose of a drug and the magnitude of the response (Fig. 2B). We calculated the probability of achieving Stage III anesthesia depth at various dexmedetomidine infusion rates (Table 4). The impact of dexmedetomidine demonstrated a correlation with dosage, with the frequency of achieving Stage III anesthesia intensifying alongside elevated rates of administration. Probit regression was used to obtain the ED50 and ED95 of dexmedetomidine infusion rate to maintain stage III anesthesia, which were 2.298 (95%CI: 2.190–2.404) μg/kg·h and 3.765 (95%CI: 3.550–4.050) μg/kg·h respectively.

The minimum HR during anesthesia maintenance was 52.0 ± 5.8 bpm. 2 patients had bradycardia (HR < 45 bpm), and their HR normalized after 0.5 mg atropine infusion. The maximum HR during maintenance was 80.3 ± 15.2 bpm. The maximum MAP during maintenance was 117.8 ± 12.8 mmHg, and maximum MAP variation percentage was 22.4 ± 15.1%. 6 patients had hypertension (SBP >180 mmHg), and their BP normalized after 100 μg nitroglycerin infusion. The minimum MAP during maintenance was 86.1 ± 12.0 mmHg and minimum MAP variation percentage was −10.8 ± 10.7%. Intraoperative PSI scores ranged from 25 to 40, HR decreased and stabilized around 60 bpm, while MAP remained relatively stable during anesthesia maintenance (Fig. 2C–E). In PACU, the minimum HR was 48.6 ± 5.1 bpm, and 6 patients experienced bradycardia, which resolved with 0.5 mg atropine infusion. The maximum HR was 57.3 ± 7.2 bpm. The minimum and maximum MAP in PACU were 89.3 ± 13.7 mmHg and 99.9 ± 14.8 mmHg respectively. The minimum and maximum HR during the first 3 postoperative hours in the ward were 53.9 ± 8.3 bpm and 67.4 ± 13.0 bpm respectively. One patient had transient bradycardia, which resolved without treatment. The minimum and maximum MAP in the ward were 83.1 ± 12.7 mmHg and 98.7 ± 13.1 mmHg respectively. No postoperative tachycardia, hypertension, or hypotension was observed. These results indicate that intraoperative dexmedetomidine infusion affected HR in the intraoperative and early post-operative period, and could be corrected with vasoactive drugs such as atropine.

The median wake-up time from general anesthesia was 4.8 min, and most patients woke up within 5 min, but one patient woke up 31 min after discontinuing anesthesia. We further analyzed the perioperative data of this patient, and found that his intraoperative maximum HR was 116 bpm and his postoperative maximum HR in the ward was 106 bpm. Then, we analyzed the relationship between HR and MAP with wake-up time and intraoperative dexmedetomidine dose. The results indicated that both intraoperative and postoperative maximum HR had significant correlation with wake-up time of patients after anesthesia (correlation coefficient, $r = 0.451$, $p = 0.012$ and $r = 0.518$, $p = 0.003$ respectively). Intraoperative, but not postoperative, maximum HR had moderate positive linear relationship with intraoperative dexmedetomidine dose ($r = 0.453$, $p = 0.012$ and $r = 0.310$, $p = 0.095$ respectively). Neither the minimum and average HR, nor the minimum, average and maximum MAP had the similar correlation (Fig. 3A–D). These results indicated the relationship between perioperative maximum HRs and wake-up time/intraoperative dexmedetomidine dose.

Table 3
DEX-led anesthesia characteristics. Data are presented as mean ± SD, median (interquartile range), or number (percentage).

DEX induction dose (μg/kg) PSI on loss of consciousness	3.1 (3, 3.4) 45.5 ± 7.7
Duration of surgery (h)	3.1 ± 0.7
Duration of anesthesia (h)	3.6 ± 0.7
Awakening time from general anesthesia (min)	4.8 (3.5, 7.2)
PSI on regain of consciousness	59.6 ± 6.3
Intraoperative DEX dose (μg/kg·h)	3.2 ± 0.8
Intraoperative remifentanil dose (μg/kg·h)	13.0 ± 2.8
Intraoperative rocuronium dose (mg/kg·h)	0.44 ± 0.08
Infusion volume (ml/kg·h)	6.6 ± 1.6
Urine volume (ml/kg·h)	1.3 (1.0, 2.2)
Bleeding volume (ml)	20 (20, 50)
PSI on leaving the operating room	87.8 ± 5.4
Postoperative agitation	0 (0.0%)
Postoperative shivering	1 (3.3%)
Postoperative SpO2 < 90%	0 (0.0%)
Postoperative nausea and vomiting	0 (0.0%)
Numeric pain rating scale on postoperative day 1	1.8 ± 1.5
Minimum HR during maintenance (bpm)	52.0 ± 5.8
Bradycardia (HR < 45 bpm)	2 (6.7%)
Maximum HR during maintenance (bpm)	80.3 ± 15.2
Minimum MAP during maintenance (mmHg)	86.1 ± 12.0
Minimum MAP variation percentage (%)d	−10.8 ± 10.7
Maximum MAP during maintenance (mmHg)	117.8 ± 12.8
Maximum MAP variation percentage (%)	22.4 ± 15.1
Hypertension (SBP >180 mmHg)	6 (20.0%)
Minimum HR in PACU (bpm)	48.6 ± 5.1
Bradycardia (HR < 45 bpm)	6 (20%)
Maximum HR in PACU (bpm)	57.3 ± 7.2
Minimum MAP in PACU (mmHg)	89.3 ± 13.7
Maximum MAP in PACU (mmHg)	99.9 ± 14.8
Minimum HR in ward for the first 3 postoperative hours (bpm)	53.9 ± 8.3
Maximum HR in ward for the first 3 postoperative hours (bpm)	67.4 ± 13.0
Minimum MAP in ward for the first 3 postoperative hours (bpm)	83.1 ± 12.7
Maximum MAP in ward for the first 3 postoperative hours (bpm)	98.7 ± 13.1
Intraoperative awareness by Modified Brice interview	
The last thing to remember before induction	
Facemask pre-oxygenation	27 (90.0%)
Call his/her name	3 (10.0%)
The first thing to remember after emergence	
Call his/her name in the operating room	24 (60.0%)
In the ward	4 (13.3%)
In the operating room	1 (3.3%)
Extubation	1 (3.3%)
Conscious or dreaming during anesthesia	0 (0.0%)
Other adverse reactions during anesthesia	0 (0.0%)
Diagnosis of delirium by Short CAM	
Acute change in mental status	0 (0.0%)
Behavior fluctuation	0 (0.0%)
Difficulty in focusing attention	0 (0.0%)
Disorganized or incoherent thinking	0 (0.0%)
Altered level of consciousness	1 (3.3%) for vigilant
Satisfaction by ISAS	
I threw up or felt like throwing up	−2.1 ± 1.2
I would want to have the same anesthetic again	3.0 ± 0.2
I itched	−3.0 ± 0
I felt relaxed	2.8 ± 0.5
I felt pain	−1.9 ± 1.1
I felt safe	3.0 ± 0.2
I was too cold or hot	−2.8 ± 0.5
I was satisfied with my anesthetic care	3.0 ± 0.2
I felt pain during surgery	−2.9 ± 0.4
I felt good	2.8 ± 0.6
I hurt	−2.9 ± 0.2

The results of Modified Brice interview showed that the last thing patients remembered before induction was calling the name (3 patients) or being preoxygenated by facemask (27 patients). The first thing patients remembered after surgery was calling name (24 patients), extubation (2 patients), or in the ward (4 patients). No intraoperative dreaming, consciousness, or serious adverse reactions

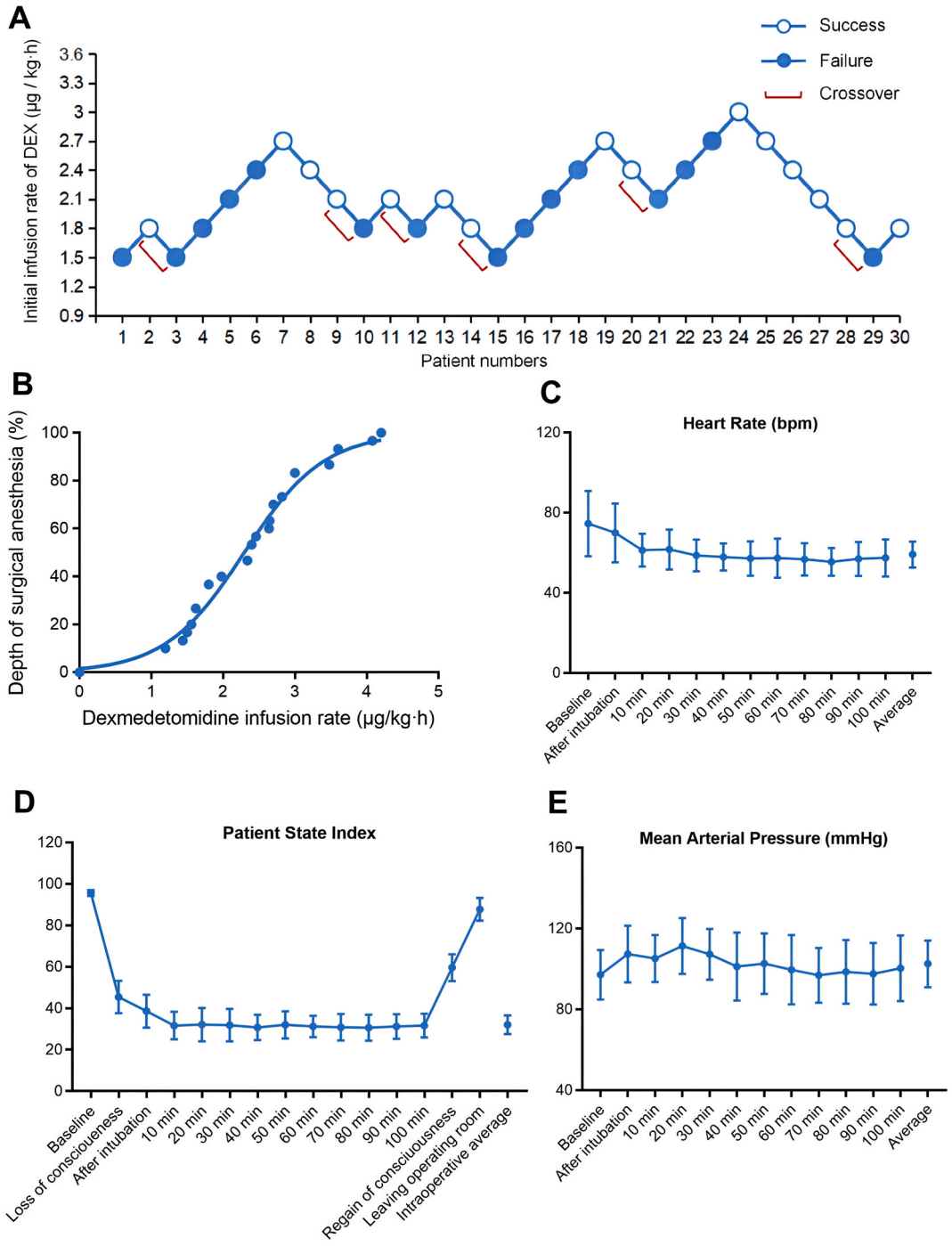


Fig. 2. **(A)** Sequence of initial infusion rate of DEX administered and subsequent response (comparison with average DEX infusion rate of 50–100 min after intubation). Success (Initial rate is greater than the average DEX infusion rate 50–100 min after intubation) – open circle; failure (Initial rate is smaller than the average DEX infusion rate 50–100 min after intubation) – filled circle. **(B)** Rate-response curve for DEX plotted using probit analysis. The ED50 and ED95 of DEX to achieve the state 'maintain the depth of major surgical anesthesia' were 2.298 μg/kg·h (95%CI: 2.190–2.404 μg/kg·h) and 3.765 μg/kg·h (95%CI: 3.550–4.050 μg/kg·h) respectively. The change trends of PSI **(C)**, HR **(D)** and MAP **(E)** of patients during anesthesia maintenance. *p < 0.05, **p < 0.01, ***p < 0.001 compared with baseline, ###p < 0.001 compared with intraoperative average PSI.

Table 4
Calculated probabilities of depth of anesthesia as stage III.

Probability	DEX infusion rate (μg/kg·h)	95% CI
0.05	0.830	0.536-1.052
0.10	1.154	0.913-1.338
0.20	1.547	1.365-1.690
0.30	1.830	1.685-1.950
0.40	2.071	1.951-2.179
0.50	2.298	2.190-2.404
0.60	2.524	2.417-2.640
0.70	2.765	2.649-2.903
0.80	3.049	2.910-3.222
0.90	3.441	3.263-3.673
0.95	3.765	3.550-4.050

was reported. CAM-S showed that one patient was vigilant and rated as 1 point in 'Altered level of consciousness', and the patients were rated as 0 point in other items. Therefore, no patient was diagnosed as postoperative delirium. Compared with previous study results [6], we inferred that the low incidence of postoperative delirium could be related to the young population and the effects of dexmedetomidine-led anesthesia strategy. ISAS satisfaction scale showed that the mean sores of 'I threw up or felt like throwing up' and 'I felt pain' were −2.1 and −1.9 respectively. The scores of other 9 questions were close or equal to full score (3). Overall, the patients were satisfied with dexmedetomidine-led general anesthesia, and the problems existed in postoperative pain and nausea management, which was related to the intravenous analgesia alone, and a combination with nerve block analgesia could improve the situation.

4. Discussion

This study showed that dexmedetomidine-led anesthesia could maintain the depth of stage III anesthesia during major abdominal surgery. The duration of anesthesia was 3.6 ± 0.7 h. The ED50 and ED95 of dexmedetomidine infusion rate during anesthesia maintenance were 2.298 μg/kg·h and 3.765 μg/kg·h respectively. The minimum HR during anesthesia maintenance, in PACU, and in ward were 52.0 ± 5.8, 48.6 ± 5.1 and 53.9 ± 8.3 bpm respectively. There were 2 patients during anesthesia and 6 patients in PACU developed bradycardia (HR < 45 bpm), and their HR returned to normal range after atropine infusion. 6 patients developed intraoperative hypertension (SBP >180 mmHg), and their BP returned to normal range after nitroglycerin infusion. The median wake-up time from general anesthesia was 4.8 min, and the perioperative maximum HR had significant correlation with wake-up time and dexmedetomidine dose. Neither intraoperative awareness nor postoperative delirium were observed, and patients' satisfaction with dexmedetomidine-led anesthesia was notably high.

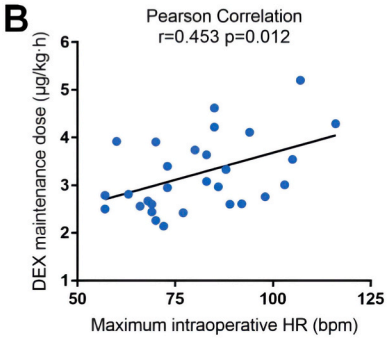
Previous study showed that dexmedetomidine at plasma concentrations of 0.37 ng/ml and 0.69 ng/ml reduced isoflurane MAC by 35% and 47%, respectively [19]. Our previous study showed that dexmedetomidine-led strategy could accomplish anesthesia induction [9]. This study showed that dexmedetomidine-led strategy also ensured effective anesthesia maintenance and adequate depth during abdominal surgery. To analyze the EEG signals during this maintenance phase, we utilized the density spectral array (DSA), which provided brain electrical activity characteristics [20]. The typical perioperative DSAs were captured (Fig. 3E–H). The white trend line represents the 95% spectral edge frequency (SEF), which reflects the sleep state of the patients [21]. The DSA before anesthesia (PSI = 95) was characterized by β, α and θ waves, and 95% SEF was around 15 Hz (Fig. 3E). The DSA during dexmedetomidine anesthesia maintenance (PSI = 35) exhibited higher level of δ wave activity, which indicated a brain state resembling deep sleep. The 95% SEF was around 3 Hz (Fig. 3F). The DSA after dexmedetomidine anesthesia (PSI = 92) was characterized by sustained high frequency brain electrical activity. The 95% SEF was around 30 Hz (Fig. 3G). To compare the differences in brain electrical activity between dexmedetomidine and propofol maintenance, we observed the DSA during propofol maintenance (PSI = 35), which was characterized by α and θ waves, and the 95% SEF was around 10–15 Hz (Fig. 3H). The 95% SEF during propofol maintenance was much higher than during dexmedetomidine maintenance. The underlying mechanisms could be related with GABAA and NMDA receptors in the cortex, thalamus, brain stem and striatum, as well as α2-adrenergic receptor in the locus ceruleus and ventrolateral preoptic nucleus [22], and required further investigation.

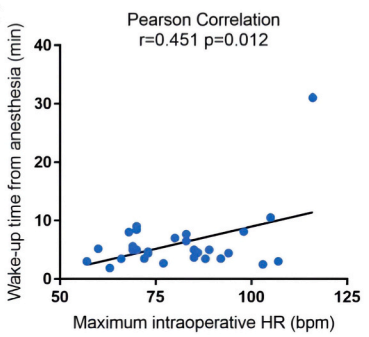
Bradycardia is a common adverse effect of dexmedetomidine, and its incidence varies from 10% to 30%, depending on dexmedetomidine dose [1]. Therefore, in this study, we excluded the patients with bradycardia, severe heart conduction block and other heart diseases. The results showed that 2 patients developed intraoperative bradycardia and 6 patients developed bradycardia in PACU, but their HR recovered rapidly after atropine infusion. One patient experienced transient bradycardia in ward and the HR recovered without treatment. There are multiple potential mechanisms for dexmedetomidine related bradycardia: 1. Dexmedetomidine activates α2 receptor in vascular smooth muscle, causes peripheral vasoconstriction and baroceptor reflex related HR decrease [23]. 2. Dexmedetomidine acts on central presynaptic and postsynaptic α2 receptors in specific brain regions involved in sleep and wakefulness regulation, such as the locus coeruleus, and impacts endogenous sleep-promoting pathways [24,25]. 3. Dexmedetomidine exerts calming and anti-anxiety effect, which is similar to the natural HR decrease during sleep [26]. 4. Dexmedetomidine induces hypertension, inhibits neural firing activity in the pontine noradrenergic nucleus of locus coeruleus, and inhibits centrally mediated sympathetic outflow. 5. Dexmedetomidine reduces the inhibition on cardiac vagus nerve and increases the excitability of

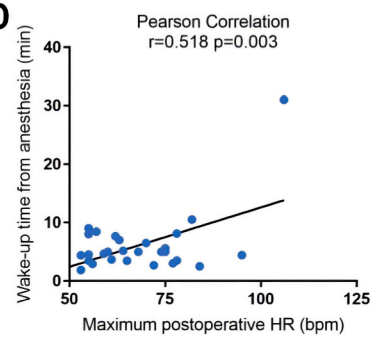
A **Pearson correlation coefficient (r) and p value**

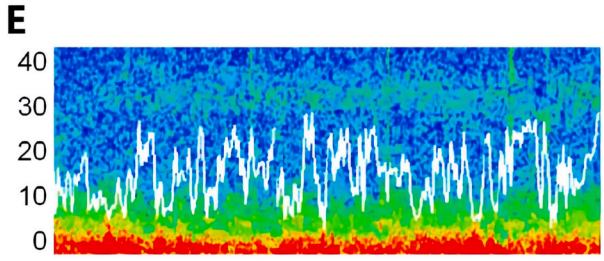
Intraoperative period						
	Minimum HR	Average HR	Maximum HR	Minimum MAP	Average MAP	Maximum MAP
Intraoperative DEX dose	r=-0.097 p=0.609	r=-0.041 p=0.829	**r=0.453 p=0.012**	r=0.105 p=0.581	r=-0.004 p=0.981	r=-0.053 p=0.780
Wake-up time from anesthesia	r=0.166 p=0.381	r=0.078 p=0.681	**r=0.451 p=0.012**	r=-0.008 p=0.967	r=-0.066 p=0.729	r=-0.003 p=0.987

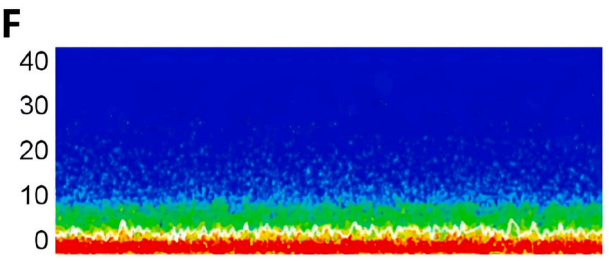
Postoperative period				
	Minimum HR	Maximum HR	Minimum MAP	Maximum MAP
Intraoperative DEX dose	r=-0.233 p=0.216	**r=0.310 p=0.095**	r=0.202 p=0.285	r=-0.095 p=0.619
Wake-up time from anesthesia	r=0.314 p=0.091	**r=0.518 p=0.003**	r=-0.054 p=0.778	r=-0.171 p=0.365

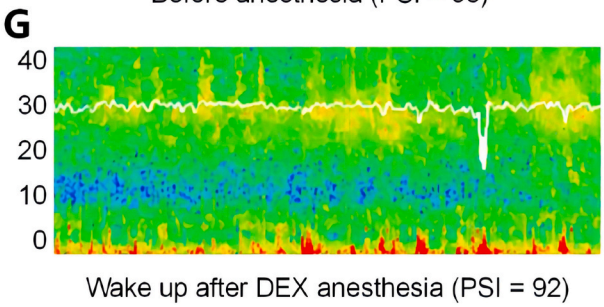












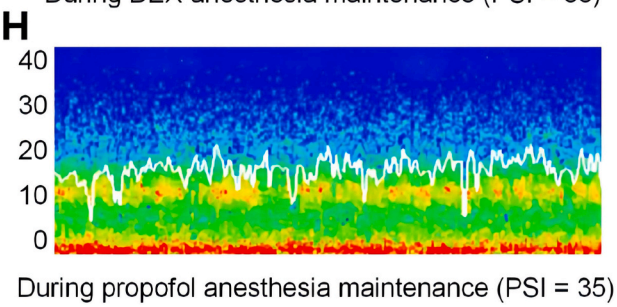


Fig. 3. (A–D) The Pearson correlation coefficient and P value between postoperative wake-up time and intraoperative DEX dose with intraoperative average HR, maximum HR, minimum HR, average MAP, maximum MAP, minimum MAP. The density spectral array in the patient before anesthesia (PSI = 95, **E**), during DEX anesthesia maintenance (PSI = 35, **F**), wake up after DEX anesthesia (**G**) and during propofol anesthesia maintenance (PSI = 35, **H**). δ waves: 0.5–4 Hz, θ waves: 4–8 Hz, α waves: 8–13 Hz, β waves: 13–30 Hz.

parasympathetic neurons projecting to heart [27], and dexmedetomidine related bradycardia could be the result of altered sympathetic-parasympathetic balance [23]. 6. Dexmedetomidine modulates ion channels in cardiac cells, such as Na + channel NaV1.5 in sinoatrial node, and results in HR decrease [28,29]. Considering the effect of dexmedetomidine on HR, when using dexmedetomidine-led anesthesia, continuous HR monitoring is necessary, and the influence of other intraoperative factors need to be considered for treatment strategy development [30]. Previous study indicated that low concentration of dexmedetomidine decreased MAP by 13%, and higher concentration of dexmedetomidine progressively increased MAP (average peak increase = 12%) [31]. Our study indicated that dexmedetomidine-led anesthesia induction and maintenance increased MAP, and the incidence of intraoperative hypertension was even higher than bradycardia. Therefore, combined remifentanil infusion was used, and BP variations were maintained at less than 20% during anesthesia maintenance.

The median wake-up time after dexmedetomidine-led anesthesia was 4.8 min, but one patient woke up 31 min after anesthesia. We analyzed his perioperative data and found that his intraoperative and postoperative maximum HR was 116 and 106 bpm respectively. We further found that perioperative maximum HR had moderate positive linear relationship between intraoperative dexmedetomidine dose and wake-up time after anesthesia ($r = 0.451$, $p = 0.012$), which indicated that perioperative HR could be a reference factor for dexmedetomidine dose adjustment and recovery management. The underlying mechanisms remain unclear. We speculate that certain patients may exhibit a weak response to the aforementioned mechanisms, such as insensitivity to α2-receptor or NaV1.5 channel, leading to relative high HR and high requirement of dexmedetomidine during anesthesia. Then, the high dose of dexmedetomidine could activate a larger quantity of GABA receptor and 5-HT1A receptor, resulting in more pronounced residual effects and delayed arousal [23,32].

Neurotoxic effects of anesthetics are potential factors that can lead to cognitive and behavioral impairments, particularly in elderly or cognitive decline patients [33]. Clinical studies indicated that the prevalence of postoperative delirium in elderly patients under sevoflurane and propofol-led anesthesia was 23.3% and 33.0%. Mechanism studies indicated that neonates could exhibit brain structural abnormalities following prolonged exposure to 2.5–4% sevoflurane [34]. Inhaled anesthetics related neurotoxicity included neurogenesis alteration, increased apoptosis and reduced proliferation of neural stem cells [35,36]. Therefore, non-injurious anesthetics and anesthesia strategy need more research. Studies indicated that dexmedetomidine improved cognitive function, and reduced isoflurane-related neuroinflammation and apoptosis through inhibiting TLR2-NF-κB pathway [37,38]. dexmedetomidine also inhibited HIF-α-PKM2 pathway, promoted PI3K-AKT pathway, and regulated the balance between cell survival and apoptosis [39,40]. The combination of dexmedetomidine and 1% sevoflurane provided similar depth of anesthesia with 2.5% sevoflurane, and was associated with reduced neuronal injury [34]. Therefore, dexmedetomidine-led anesthesia could be potential non-injurious anesthesia strategy. The present study provided a feasible dexmedetomidine-led anesthesia strategy in healthy adults, and our preliminary experiment indicated that elderly patients needed much lower dexmedetomidine infusion rate in anesthesia maintenance, and had short postoperative wake-up time and better cognitive function than inhaled anesthesia. Additional research is imperative to refine the dexmedetomidine-centered anesthesia approach for elderly patients or those with cognitive decline.

Previous study indicated that as an anesthesia adjunct, dexmedetomidine prolonged anesthesia emergence [41], but this study indicated that the emergence time of dexmedetomidine-led anesthesia was 4.8 min, which was shorter than short-duration anesthetic propofol (emergence time, 5.9 min) and desflurane (emergence time, 5.7 min) [42]. We provided intensive anesthesia depth monitoring during maintenance and no intraoperative awareness events occurred, but based on Wilson confidence interval calculation, the upper confidence limit of occurrence rate of intraoperative awareness was 3.27% (sample size = 30). The current rate of intraoperative awareness in clinical practice was 0.3% [43], and considered the rate of 3.27% and 0.3%, a non-inferiority study of intraoperative awareness for dexmedetomidine-led anesthesia is further required, which needs at least 1131 candidates. The combination of dexmedetomidine with low doses of sevoflurane or midazolam during maintenance could reduce the possibility of intraoperative awareness, which requires verification by subsequent studies. Previous study indicated that combined 1.2 μg/ml (target plasma concentration) propofol decreased the inhaled concentration of sevoflurane to 0.3 MAC in anesthesia maintenance and provided faster awakening and extubation [44]. The combination of dexmedetomidine and inhaled anesthetic could provide faster awakening, as well as better postoperative cognitive function and lower incidence of delirium [45], and it could be valuable for elderly and cognitive decline patients. This study provided the ED50 of dexmedetomidine infusion rate in maintenance, which could be a dose reference for potential combined anesthesia implementation.

There are several limitations. Firstly, this study revealed a dexmedetomidine-led anesthesia maintenance strategy with controllable effects on HR and BP. But the results were limited in ASA I or II patients without surgical complications. Assessing the safety and therapeutic effectiveness of this modality across diverse patient populations and clinical contexts is imperative prior to its integration into routine clinical application. Secondly, anesthesia maintenance was achieved by infusing both dexmedetomidine and remifentanil, so the outcomes reflect the effective dose in the combination rather than dexmedetomidine alone. Thirdly, short-CAM is a widely used assessment tool for delirium, but it focuses on specific criteria, so a combination of CAM with other tools, such as DRS-R-98, Mini-Cog, etc., could be better for delirium diagnosis. Fourthly, this study suggested that perioperative maximal heart rate could serve as a reference for adjusting dexmedetomidine dosage and predict wake-up time in dexmedetomidine-led anesthesia. However, further investigation is needed to reveal the underlying mechanisms.

5. Conclusion

This study showed that dexmedetomidine-led anesthesia could maintain the depth of stage III anesthesia during major abdominal surgery. The ED50 and ED95 of dexmedetomidine infusion rate during anesthesia maintenance were 2.298 μg/kg·h and 3.765 μg/kg·h respectively. Perioperative maximum HR had significant correlation with intraoperative dexmedetomidine dose and wake-up time

from anesthesia. Further studies are required to assess the feasibility and benefits of dexmedetomidine-led anesthesia in elderly or cognitive decline patients, and explore the valuable combined anesthesia strategies with dexmedetomidine.

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Data availability statement

The data of the patients in this study are not publicly available due to the ethical restriction, and they are available on request from the corresponding author.

CRediT authorship contribution statement

Cheng Ni: Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Wenjie Xu:** Writing – original draft, Formal analysis, Data curation. **Bing Mu:** Writing – review & editing, Methodology, Data curation. **Hongyi Li:** Writing – review & editing, Investigation. **Jiao Geng:** Writing – review & editing, Formal analysis. **Yinyin Qu:** Writing – review & editing, Conceptualization. **Yi Tian:** Investigation, Data curation. **Jie Yu:** Writing – review & editing, Project administration. **Naiyuan Tian:** Writing – review & editing, Project administration. **Xiaoxiao Wang:** Software, Methodology. **Chan Chen:** Writing – review & editing, Supervision. **Xu Jin:** Writing – review & editing, Supervision. **Hui Zheng:** Writing – review & editing, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26983.

References

[1] Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, et al., Early sedation with dexmedetomidine in critically ill patients, N. Engl. J. Med. 380 (2019) 2506–2517, https://doi.org/10.1056/NEJMoa1904710.
[2] Y. Skrobik, M.S. Duprey, N.S. Hill, J.W. Devlin, Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial, Am. J. Respir. Crit. Care Med. 197 (2018) 1147–1156, https://doi.org/10.1164/rccm.201710-1995OC.
[3] Y. Hu, H. Zhou, H. Zhang, Y. Sui, Z. Zhang, Y. Zou, K. Li, Y. Zhao, J. Xie, L. Zhang, The neuroprotective effect of dexmedetomidine and its mechanism, Front. Pharmacol. 13 (2022) 965661, https://doi.org/10.3389/fphar.2022.965661.
[4] W.H. Tao, X.S. Shan, J.X. Zhang, H.Y. Liu, B.Y. Wang, X. Wei, M. Zhang, K. Peng, J. Ding, S.X. Xu, et al., Dexmedetomidine attenuates ferroptosis-mediated renal ischemia/reperfusion injury and inflammation by inhibiting ACSL4 via α2-AR, Front. Pharmacol. 13 (2022) 782466, https://doi.org/10.3389/fphar.2022.782466.
[5] H. Li, C. Lu, W. Yao, L. Xu, J. Zhou, B. Zheng, Dexmedetomidine inhibits inflammatory response and autophagy through the circLrp1b/miR-27a-3p/Dram 2 pathway in a rat model of traumatic brain injury, Aging 12 (2020) 21687–21705, https://doi.org/10.18632/aging.103975.
[6] X. Su, Z.T. Meng, X.H. Wu, F. Cui, H.L. Li, D.X. Wang, X. Zhu, S.N. Zhu, M. Maze, D. Ma, Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial, Lancet 388 (2016) 1893–1902, https://doi.org/10.1016/S0140-6736(16)30580-3.
[7] F. Xu, L. Han, Y. Wang, D. Deng, Y. Ding, S. Zhao, Q. Zhang, L. Ma, X. Chen, Prolonged anesthesia induces neuroinflammation and complement-mediated microglial synaptic elimination involved in neurocognitive dysfunction and anxiety-like behaviors, BMC Med. 21 (2023) 7, https://doi.org/10.1186/s12916-022-02705-6.
[8] L.J. O'Bryan, K.J. Atkins, A. Lipszyc, D.A. Scott, B.S. Silbert, L.A. Evered, Inflammatory biomarker levels after propofol or sevoflurane anesthesia: a meta-analysis, Anesth. Analg. 134 (2022) 69–81, https://doi.org/10.1213/ane.0000000000005671.
[9] B. Mu, W. Xu, H. Li, Z. Suo, X. Wang, Y. Zheng, Y. Tian, B. Zhang, J. Yu, N. Tian, et al., Determination of the effective dose of dexmedetomidine to achieve loss of consciousness during anesthesia induction, Front. Med. 10 (2023) 1158085, https://doi.org/10.3389/fmed.2023.1158085.
[10] B.C. Bloor, D.S. Ward, J.P. Belleville, M. Maze, Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes, Anesthesiology 77 (1992) 1134–1142, https://doi.org/10.1097/00000542-199212000-00014.
[11] P.R. Housmans, Effects of dexmedetomidine on contractility, relaxation, and intracellular calcium transients of isolated ventricular myocardium, Anesthesiology 73 (1990) 919–922, https://doi.org/10.1097/00000542-199011000-00020.
[12] M.H. Møller, W. Alhazzani, K. Lewis, E. Belley-Cote, A. Granholm, J. Centofanti, W.B. McIntyre, J. Spence, Z. Al Duhailib, D.M. Needham, et al., Use of dexmedetomidine for sedation in mechanically ventilated adult ICU patients: a rapid practice guideline, Intensive Care Med. 48 (2022) 801–810, https://doi.org/10.1007/s00134-022-06660-x.
[13] J.W. Sleigh, S. Vacas, A.M. Flexman, P.O. Talke, Electroencephalographic arousal patterns under dexmedetomidine sedation, Anesth. Analg. 127 (2018) 951–959, https://doi.org/10.1213/ane.0000000000003590.
[14] R.R. Riker, Y. Shehabi, P.M. Bokesch, D. Ceraso, W. Wisemandle, F. Koura, P. Whitten, B.D. Margolis, D.W. Byrne, E.W. Ely, M.G. Rocha, Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial, JAMA 301 (2009) 489–499, https://doi.org/10.1001/jama.2009.56.

[15] D. Drover, H.R. Ortega, Patient state index, Best Pract. Res. Clin. Anaesthesiol. 20 (2006) 121–128, https://doi.org/10.1016/j.bpa.2005.07.008.
[16] Y. Kasuya, R. Govinda, S. Rauch, E.J. Mascha, D.I. Sessler, A. Turan, The correlation between bispectral index and observational sedation scale in volunteers sedated with dexmedetomidine and propofol, Anesth. Analg. 109 (2009) 1811–1815, https://doi.org/10.1213/ANE.0b013e3181c04e58.
[17] G.A. Mashour, C. Kent, P. Picton, S.K. Ramachandran, K.K. Tremper, C.R. Turner, A. Shanks, M.S. Avidan, Assessment of intraoperative awareness with explicit recall: a comparison of 2 methods, Anesth. Analg. 116 (2013) 889–891, https://doi.org/10.1213/ANE.0b013e318281e9ad.
[18] W.J. Dixon, Staircase bioassay: the up-and-down method, Neurosci. Biobehav. Rev. 15 (1991) 47–50, https://doi.org/10.1016/s0149-7634(05)80090-9.
[19] R. Aantaa, M.-L. Jaakola, A. Kallio, J. Kanto, Reduction of the minimum alveolar concentration of isoflurane, Dexmedetomidine Anesthesiology 86 (1997) 1055–1060, https://doi.org/10.1097/00000542-199705000-00008.
[20] Y.W. Ni, P.N. Chen, J. Tse, Density spectral array as an additional sedative indicator, J. Anesth. 36 (2022) 444, https://doi.org/10.1007/s00540-022-03064-5.
[21] D. Nieuwenhuijs, E.L. Coleman, N.J. Douglas, G.B. Drummond, A. Dahan, Bispectral index values and spectral edge frequency at different stages of physiologic sleep, Anesth. Analg. 94 (2002) 125–129, https://doi.org/10.1097/00000539-200201000-00024, table of contents.
[22] C. Xi, S. Sun, C. Pan, F. Ji, X. Cui, T. Li, Different effects of propofol and dexmedetomidine sedation on electroencephalogram patterns: wakefulness, moderate sedation, deep sedation and recovery, PLoS One 13 (2018) e0199120, https://doi.org/10.1371/journal.pone.0199120.
[23] M.A.S. Weerink, M. Struys, L.N. Hannivoort, C.R.M. Barends, A.R. Absalom, P. Colin, Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine, Clin. Pharmacokinet. 56 (2017) 893–913, https://doi.org/10.1007/s40262-017-0507-7.
[24] S. Schwerin, C. Westphal, C. Klug, G. Schneider, M. Kreuzer, R. Haseneder, S. Kratzer, Sedative properties of dexmedetomidine are mediated independently from native thalamic hyperpolarization-activated cyclic nucleotide-gated channel function at clinically relevant concentrations, Int. J. Mol. Sci. 24 (2022), https://doi.org/10.3390/ijms24010519.
[25] L.E. Nelson, J. Lu, T. Guo, C.B. Saper, N.P. Franks, M. Maze, The alpha 2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects, Anesthesiology 98 (2003) 428–436, https://doi.org/10.1097/00000542-200302000-00024.
[26] Y.W. Hsu, L.I. Cortinez, K.M. Robertson, J.C. Keifer, S.T. Sum-Ping, E.W. Moretti, C.C. Young, D.R. Wright, D.B. Macleod, J. Somma, Dexmedetomidine pharmacodynamics: part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers, Anesthesiology 101 (2004) 1066–1076, https://doi.org/10.1097/00000542-200411000-00005.
[27] D.B. Sharp, X. Wang, D. Mendelowitz, Dexmedetomidine decreases inhibitory but not excitatory neurotransmission to cardiac vagal neurons in the nucleus ambiguus, Brain Res. 1574 (2014) 1–5, https://doi.org/10.1016/j.brainres.2014.06.010.
[28] C. Stoetzer, S. Reuter, T. Doll, N. Foadi, F. Wegner, A. Leffler, Inhibition of the cardiac Na^+ channel α-subunit Nav 1.5 by propofol and dexmedetomidine, N. Schmied. Arch. Pharmacol. 389 (2016) 315–325, https://doi.org/10.1007/s00210-015-1195-1.
[29] B.S. Chen, H. Peng, S.N. Wu, Dexmedetomidine, an alpha 2-adrenergic agonist, inhibits neuronal delayed-rectifier potassium current and sodium current, Br. J. Anaesth. 103 (2009) 244–254, https://doi.org/10.1093/bja/aep107.
[30] D. Kang, C. Lim, D.J. Shim, H. Kim, J.W. Kim, H.J. Chung, Y. Shin, J.D. Kim, S.J. Ryu, The correlation of heart rate between natural sleep and dexmedetomidine sedation, Korean journal of anesthesiology 72 (2019) 164–168, https://doi.org/10.4097/kja.d.18.00208.
[31] T.J. Ebert, J.E. Hall, J.A. Barney, T.D. Uhrich, M.D. Colinco, The effects of increasing plasma concentrations of dexmedetomidine in humans, Anesthesiology 93 (2000) 382–394, https://doi.org/10.1097/00000542-200008000-00016.
[32] A. Newman-Tancredi, J.P. Nicolas, V. Audinot, S. Gavaudan, L. Verrièle, M. Touzard, C. Chaput, N. Richard, M.J. Millan, Actions of alpha 2 adrenoceptor ligands at alpha2A and 5-HT1A receptors: the antagonist, atipamezole, and the agonist, dexmedetomidine, are highly selective for alpha2A adrenoceptors, N. Schmied. Arch. Pharmacol. 358 (1998) 197–206, https://doi.org/10.1007/pl00005243.
[33] C.E. Creeley, From drug-induced developmental neuroapoptosis to pediatric anesthetic neurotoxicity-where are we now? Brain Sci. 6 (2016) https://doi.org/10.3390/brainsci6030032.
[34] J.R. Lee, B. Joseph, R.D. Hofacer, B. Upton, S.Y. Lee, L. Ewing, B. Zhang, S.C. Danzer, A.W. Loepke, Effect of dexmedetomidine on sevoflurane-induced neurodegeneration in neonatal rats, Br. J. Anaesth. 126 (2021) 1009–1021, https://doi.org/10.1016/j.bja.2021.01.033.
[35] Q. Wang, Y. Li, H. Tan, Y. Wang, Sevoflurane-Induced apoptosis in the mouse cerebral cortex follows similar characteristics of physiological apoptosis, Front. Mol. Neurosci. 15 (2022) 873658, https://doi.org/10.3389/fnmol.2022.873658.
[36] Z.J. Bosnjak, S. Logan, Y. Liu, X. Bai, Recent insights into molecular mechanisms of propofol-induced developmental neurotoxicity: implications for the protective strategies, Anesth. Analg. 123 (2016) 1286–1296, https://doi.org/10.1213/ane.0000000000001544.
[37] K. Wang, M. Wu, J. Xu, C. Wu, B. Zhang, G. Wang, D. Ma, Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis, Br. J. Anaesth. 123 (2019) 777–794, https://doi.org/10.1016/j.bja.2019.07.027.
[38] X. Pang, P. Zhang, Y. Zhou, J. Zhao, H. Liu, Dexmedetomidine pretreatment attenuates isoflurane-induced neurotoxicity via inhibiting the TLR2/NF-κB signaling pathway in neonatal rats, Exp. Mol. Pathol. 112 (2020) 104328, https://doi.org/10.1016/j.yexmp.2019.104328.
[39] F. Bao, X. Kang, Q. Xie, J. Wu, HIF-α/PKM2 and PI3K-AKT pathways involved in the protection by dexmedetomidine against isoflurane or bupivacaine-induced apoptosis in hippocampal neuronal HT22 cells, Exp. Ther. Med. 17 (2019) 63–70, https://doi.org/10.3892/etm.2018.6956.
[40] Y. Tan, X. Bi, Q. Wang, Y. Li, N. Zhang, J. Lao, X. Liu, Dexmedetomidine protects PC12 cells from lidocaine-induced cytotoxicity via downregulation of Stathmin 1, Drug Des. Dev. Ther. 13 (2019) 2067–2079, https://doi.org/10.2147/dddt.S199572.
[41] J.K. Makkar, N. Bhatia, I. Bala, D. Dwivedi, P.M. Singh, A comparison of single dose dexmedetomidine with propofol for the prevention of emergence delirium after desflurane anaesthesia in children, Anaesthesia 71 (2016) 50–57, https://doi.org/10.1111/anae.13230.
[42] I. Kawagoe, M. Hayashida, D. Satoh, C. Mitaka, Comparison of desflurane and propofol in the speed and the quality of emergence from anesthesia in patients undergoing lung cancer surgery-a prospective, randomized study, Transl. Cancer Res. 11 (2022) 736–744, https://doi.org/10.21037/tcr-21-2635.
[43] G.A. Mashour, M.S. Avidan, Intraoperative awareness: controversies and non-controversies, Br. J. Anaesth. 115 (Suppl 1) (2015) i20–i26, https://doi.org/10.1093/bja/aev034.
[44] C. Liang, M. Ding, F. Du, J. Cang, Z. Xue, Sevoflurane/propofol coadministration provides better recovery than sevoflurane in combined general/epidural anesthesia: a randomized clinical trial, J. Anesth. 28 (2014) 721–726, https://doi.org/10.1007/s00540-014-1803-0.
[45] M. Shukry, M.C. Clyde, P.L. Kalarickal, U. Ramadhyani, Does dexmedetomidine prevent emergence delirium in children after sevoflurane-based general anesthesia? Paediatr. Anaesth. 15 (2005) 1098–1104, https://doi.org/10.1111/j.1460-9592.2005.01660.x.