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CLINICAL TRIAL REPORT

Effect of Intravenous Dexmedetomidine Premedication on Sufentanil Median Effective Concentration During Tracheal Intubation in Obese Patients: A Randomized Controlled Study

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Purpose: Sufentanil is a potent opioid analgesic frequently used to suppress the tracheal intubation response. The pathophysiological changes of obesity may affect opioid pharmacokinetics and increase the risk of opioid-induced adverse effects. Dexmedetomidine as an adjunct to anesthetic induction could save the dosage of sufentanil and attenuate hemodynamic response to tracheal intubation. This study was aimed at investigating the effect of intravenous dexmedetomidine premedication on the median effective concentration (EC50) of sufentanil for tracheal intubation in obese patients.

Patients and Methods: Fifty obese patients undergoing elective bariatric or non-bariatric surgery under general anesthesia with tracheal intubation were equally randomized into the dexmedetomidine group and the saline group. Depending on the group, the patients were intravenously premedicated with 1 μg/kg dexmedetomidine or saline before anesthesia induction. Anesthesia was induced with target-controlled infusion of propofol (at 3.5 μg/mL) and sufentanil. The effect-site concentration of sufentanil for the first patient in the two groups was set at 0.4 ng/mL. The concentration of sufentanil for the next patient was determined using Dixon's up-and-down sequential method with an interval of 0.05 ng/mL, according to the responses of the previous patient. Hemodynamic variables and sufentanil dose were recorded. The EC50 and 95% confidence interval (CI) of sufentanil were determined using probit regression analysis.

Results: The EC50 of sufentanil and 95% CI were 0.25 (95% CI, 0.17–0.31) ng/mL in the dexmedetomidine group and 0.43 (95% CI, 0.34–0.46) ng/mL in the saline group ($P < 0.05$). The dosage of sufentanil was significantly lower in the former than in the latter. The hemodynamics were stable in both groups during the study.

Conclusion: Intravenous premedication with 1 μg/kg dexmedetomidine significantly decreased the EC50 of sufentanil and sufentanil requirement for tracheal intubation in obese patients.

Keywords: dexmedetomidine, median effective concentration, sufentanil, obesity

Introduction

According to the latest data, the prevalence of obesity has increased worldwide.[1] Surgical procedures including bariatric and non-bariatric surgery in obese patients have also increased over the past few years.[2] Obese patients commonly have comorbidities like hypertension, diabetes mellitus and cardiovascular diseases.[3] Tracheal intubation is routinely performed for obese patients undergoing surgery, and it can elicit significantly adverse hemodynamic responses.[4] In addition, the higher sympathetic nervous activity in obese patients may lead to potential cardiovascular risks during tracheal intubation.[5,6] Therefore, it is important to attenuate the hemodynamic responses arising from tracheal intubation in obese patients.

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Sufentanil can provide hemodynamic stability and is commonly used to attenuate cardiovascular reactions during tracheal intubation.[7] However, sufentanil may also increase perioperative complications and impair the quality of postoperative recovery.[8] The most serious adverse effect for opioids is opioid-induced respiratory depression,[9] which can lead to hypoxemia and increased perioperative morbidity and mortality in the general population.[10] The risk of opioid-induced respiratory depression is increased by obesity-related physiological changes and the coexisting cardiorespiratory diseases in obese patients.[11] Dexmedetomidine is widely used in clinical practice, its perioperative use improves postoperative analgesia and reduces opioid consumption.[12,13] Dexmedetomidine also reportedly helps prevent fluctuations in hemodynamics during tracheal intubation.[14] Therefore, a combination of dexmedetomidine and sufentanil may achieve stable hemodynamics during tracheal intubation. Given the increased opioid sensitivity in obese patients, reducing the dose of sufentanil can not only enhance the safety of anesthesia but also help mitigate opioid-related adverse effects and improve postoperative recovery. However, little is known about the effect of dexmedetomidine on the median effective concentration (EC50) of sufentanil for tracheal intubation in obese patients. Therefore, we conducted this randomized, double-blind, up-and-down sequential allocation study to determine the EC50 of sufentanil in obese patients undergoing tracheal intubation who received intravenous premedication with 1-μg/kg dexmedetomidine.

Materials and Methods

Ethics and Trial Registration

This was a prospective, randomized, double-blind, and up-and-down sequential allocation trial. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Approval No. 2024ER198-1) on 3 April 2024 and registered with the Chinese Clinical Trials Registry (available at http://www.chictr.org.cn; identifier: ChiCTR2400085106) on 31 May 2024, and written informed consent was obtained from all patients.

Inclusion and Exclusion Criteria

From June 2, 2024, to July 31, 2024, fifty patients with American Society of Anesthesiologists physical status II–III, age 18–65 years, and body mass index (BMI) ≥ 30 kg/m^2 who were scheduled to undergo elective bariatric or non-bariatric surgery were enrolled in this study. Patients with serious cardiopulmonary disease, abnormal liver and kidney function, predicted difficult airway, known allergy to general anesthetics or dexmedetomidine, or recent use of any medication affecting the sympathetic adrenergic system or hemodynamics were excluded. Patients were withdrawn from the study if they developed bradycardia [heart rate < 50 beats/min] or hypotension [mean arterial blood pressure < 50 mmHg] requiring the administration of atropine or ephedrine.

Randomization and Blinding

All eligible patients were assigned to the dexmedetomidine group or the saline group using computer-generated randomization. An independent research nurse prepared the study solutions. The dexmedetomidine group received intravenous premedication with 1 μg/kg dexmedetomidine [Jiangsu Nhwa Pharmaceutical Co., Ltd, China.] diluted with 0.9% saline to a final volume of 20 mL; dexmedetomidine dose was calculated based on lean body weight (LBW).[15] Conversely, the saline group received the same volume of normal saline before anesthesia induction. The dose of dexmedetomidine or saline was administered over a period of 10 min. All patients and investigators were blinded to the group allocation.

Anesthetic Procedures

All patients fasted for at least 8 h and received no preoperative premedication. Routine monitoring of the following parameters was started after the patient entered the operating room: heart rate (HR), noninvasive mean arterial pressure (MAP), oxygen saturation (pulse oximetry), electrocardiogram, cerebral state index (CSI), and muscle relaxant monitoring (train of four, TOF). 18-Gauge IV cannulas were placed in the left arm vein, and 5 mL/kg Ringer's lactate solution

was infused. Oxygen was administered via an oxygen mask at 5 L/min, and oxygen saturation was maintained at 98% – 100% during dexmedetomidine or saline administration and anesthesia induction.

Anesthesia was induced with propofol target-controlled infusion (TCI, Marsh model)[16] with an effect-site concentration (Ce) of 3.5 μg/mL[17] and sufentanil TCI (Gepts model)[18] using a two-channel TCI pump (TCI-III-B, Guangxi VERYARK Technology Co., Ltd, China). Based on a previous study, the Ce of sufentanil for the first patient in both groups was set at 0.4 ng/mL.[19] When the target concentration of propofol and sufentanil was reached, 0.9 mg/kg rocuronium (dosage based on ideal body weight) was administered to facilitate tracheal intubation.

When the CSI value reached within 40–60 and TOF count reached 0, tracheal intubation was performed by an experienced anesthesiologist using the video laryngoscope within 30s. Mechanical ventilation was initiated after intubation with 100% oxygen (tidal volume of 8 mL/kg, frequency of 10–14 breaths/min). HR and MAP were recorded at 1-min intervals during the 3 min before pumping dexmedetomidine or saline, and the mean of these three values was defined as the baseline value of each patient before pumping. The values of HR and MAP during dexmedetomidine or saline pumping and anesthesia induction and at 1, 2, and 3 min after tracheal intubation were also recorded. After the trial, anesthesia was conducted by the attending anesthesiologist according to his preferred protocol. After the surgery, the patient was taken to the post-anesthesia care unit (PACU) for mechanical ventilation and awakening treatment. After extubation, all patients were routinely monitored and given oxygen through a nasal cannula or face mask in the PACU. No cases of hypoxemia were reported by anesthesia nurses or surgeons.

Determination of EC50

Dixon's up-and-down sequential allocation method was used to determine the EC50 of sufentanil.[20] The Ce of sufentanil was set at 0.4 ng/mL for the first patient in each group. For the next patient, it was decreased by a gradient of 0.05 ng/mL when the previous patient showed a negative response (an increase of HR and MAP < 20% of the baseline value), and it was increased by 0.05 ng/mL if a positive response (an increase of HR or MAP ≥ 20% of the baseline value) to tracheal intubation was noted within 3 min. The experiment was terminated after six crossovers were obtained.

Statistical Analysis

Several studies have reported the need for 20–40 patients for the Dixon up-and-down method.[21–23] Thus, we ensured a sample size of 25 patients per group. Data analysis was conducted using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Initially, all data were tested for normal distribution using the Shapiro–Wilk test, which is appropriate for small sample sizes ($n < 50$). Normally distributed continuous data were presented as mean ± standard deviation (SD). For non-normally distributed data, median and interquartile ranges were reported. Discrete data were presented as numbers. Continuous data were analyzed by Student's *t*-test or rank tests. For discrete data, frequencies and categorical outcomes were analyzed using the Fisher's exact test. We used repeated measures ANOVA to measure the differences in HR and MAP over the time and between groups. The median effective concentration (EC50) and 95% confidence intervals (CI) of sufentanil were calculated using probit regression analysis. Differences in EC50 values between groups were compared using the Mann–Whitney *U*-test. A significance level of $P < 0.05$ was used for all tests, indicating statistical significance.

Results

Fifty obese patients undergoing elective bariatric or non-bariatric surgery were enrolled in this study. Two patients were withdrawn from the study due to a mean arterial pressure (MAP) lower than 50 mmHg in the dexmedetomidine group, and 12 patients did not receive the allocated intervention in either group. Ultimately, 36 patients completed the study protocol and were analyzed (Figure 1). In total, six crossovers were observed: 19 patients in the dexmedetomidine group and 17 in the saline group (Figure 2). The two patient groups had comparable basic characteristics, with no significant differences in sex, age, height, weight metrics (ideal body weight, total weight, lean body weight, and adjusted body weight), BMI, or ASA status (Table 1). We focused on the immediate hemodynamic response up to 3 min after tracheal intubation on the basis of previous studies that have shown peak hemodynamic changes occurring within the first minute post-intubation and stabilizing by 3 min.[24] The changes in HR and MAP within this timeframe were summarized in

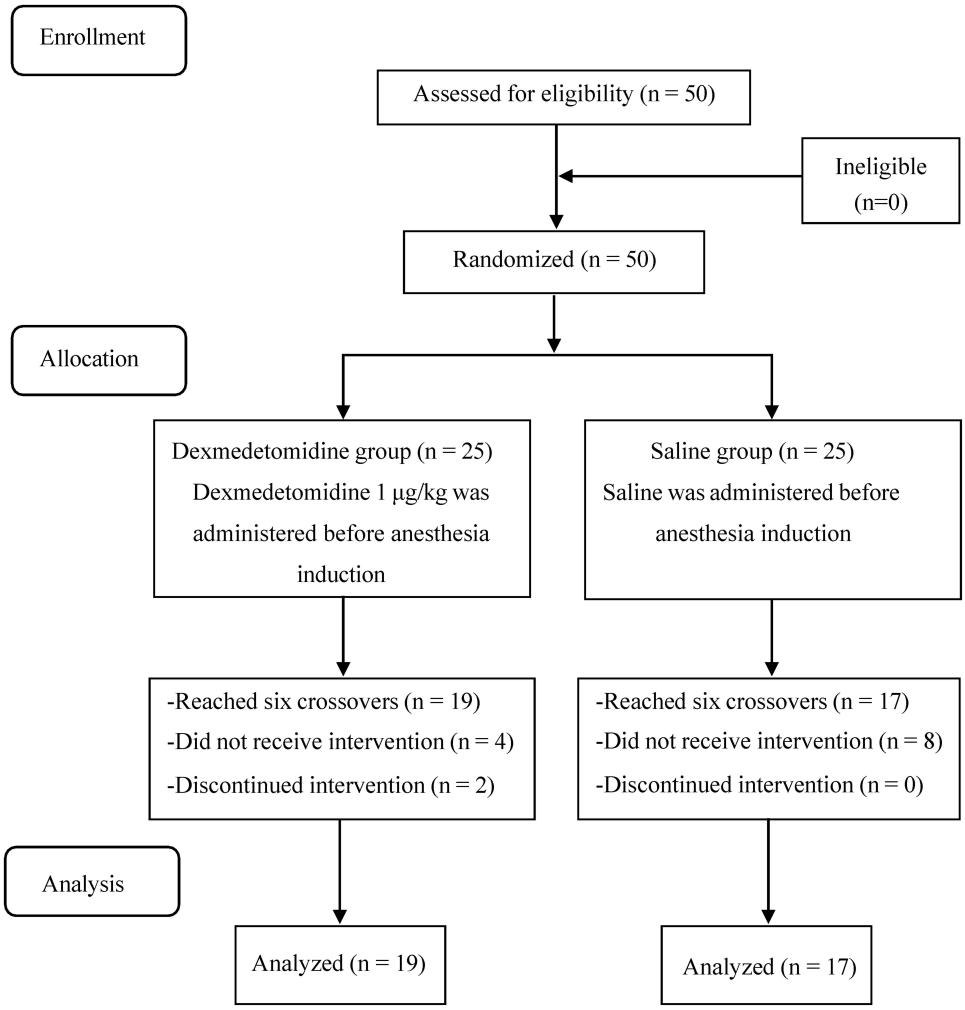

Figure 1 Consort flow diagram.

Table 2. At baseline, there were no significant differences in MAP and HR values. The peak HR and MAP values were observed within the first minute after intubation and gradually declined in both groups. The HR was significantly lower in the dexmedetomidine group compared to the saline group after intubation, indicating a notable impact of dexmedetomidine on heart rate regulation during intubation (Table 2). In contrast, the changes in MAP after intubation did not significantly differ between the two groups, indicating that dexmedetomidine had minimal impact on blood pressure regulation post-intubation.

Regarding the usage of sufentanil, the dose required was significantly lower in the dexmedetomidine group than in the saline group (Table 3), reflecting the analgesic-sparing effect of dexmedetomidine. The EC50 of sufentanil was significantly reduced in the dexmedetomidine group (0.25 ng/mL, 95% CI: 0.17–0.31 ng/mL) compared to the saline group (0.43 ng/mL, 95% CI: 0.34–0.46 ng/mL), with a statistically significant difference ($P < 0.001$) (Table 4). This result indicates that dexmedetomidine significantly reduces the EC50 of sufentanil required for tracheal intubation in obese patients.

Discussion

To our knowledge, this is the first study to assess the effect of intravenous dexmedetomidine premedication on the EC50 of sufentanil for tracheal intubation in obese patients. The results showed that intravenous premedication with 1 μg/kg dexmedetomidine before anesthesia induction decreased the EC50 of sufentanil for tracheal intubation by 41.9%. Consequently, dexmedetomidine premedication could effectively reduce the requirement for sufentanil. This finding

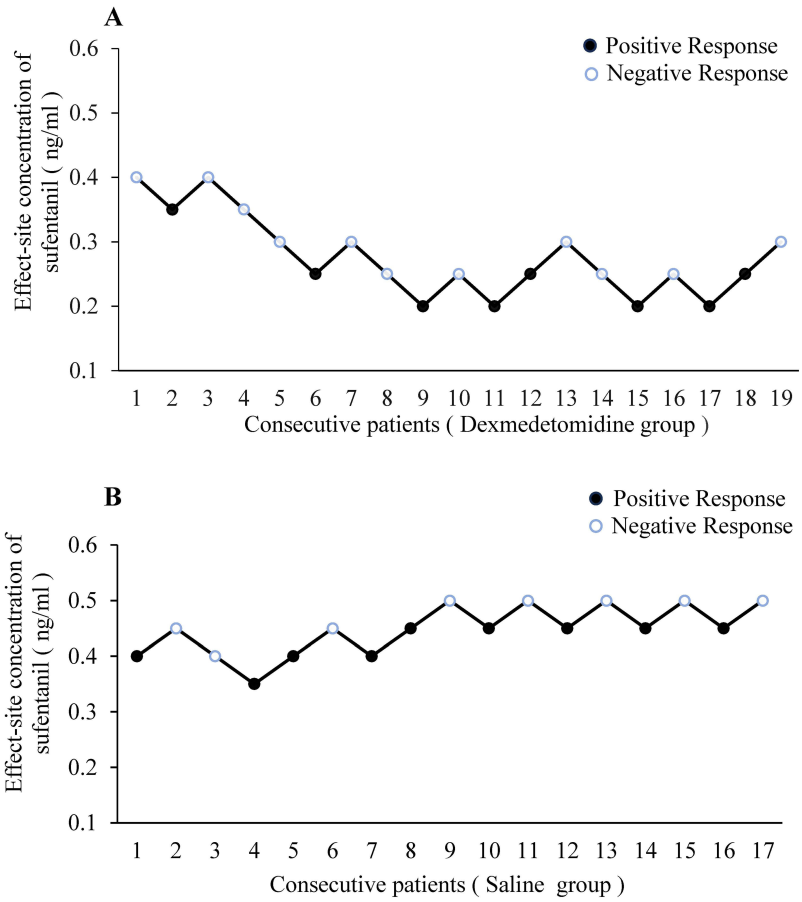

Figure 2 Sequences of effect-site concentration of sufentanil in dexmedetomidine (**A**) and saline groups (**B**). The concentration of sufentanil was determined according to the Dixon's up-and-down method.

aligns with the study objective of minimizing opioid use while maintaining adequate anesthesia, particularly in populations at risk of opioid-related complications, such as obese patients.

Although sufentanil can attenuate the adverse hemodynamic fluctuations during intubation, high dosage of sufentanil shows markedly suppressed cardiovascular and respiratory effects. This underscores the importance of finding alternative strategies to reduce opioid dosages without compromising patient safety or surgical conditions. When an opioid minimization strategy needs to be implemented under certain circumstances, such as awake tracheal intubation, spontaneous respiration via a laryngeal mask, and patients with obesity, the use of other opioid-free anesthetics, such

Table 1 Basic Characteristics of Patients

Variables	Dexmedetomidine Group (n = 19)	Saline Group (n = 17)	*P*-Value
Age (years)	31.3 ± 8.7	29.4 ± 8.7	0.536
Gender (female/male)	12/7	12/5	0.732
Height (cm)	161.0 (158.0–163.3)	163.0 (161.0–167.0)	0.075
TBW (kg)	87.0 (79.5–90.0)	89.7 (83.5–100.0)	0.183
IBW (kg)	55.0 (53.0–60.0)	58.0 (56.0–65.0)	0.172

(*Continued*)

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Table 1 (Continued).

Variables	Dexmedetomidine Group (n = 19)	Saline Group (n = 17)	*P*-Value
ABW (kg)	67.8 (65.4–70.5)	72.8 (67.6–79.4)	0.199
LBW (kg)	49.3 (47.8–52.0)	56.6 (49.7–61.9)	0.071
BMI (kg/m^2)	33.6 (31.1–36.3)	35.2 (31.2–37.2)	0.485
ASA class (II/III)	11/8	9/8	1.000

Notes: Data are presented as mean ± SD, median (interquartile range), or number, as appropriate.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; IBW, ideal body weight; TBW, total body weight; ABW, adjusted body weight; LBW, lean body weight.

Table 2 HR and MAP Values at Different Time Points for the Two Groups

Variables	Dexmedetomidine Group (n = 19)	Saline Group (n = 17)	*P*-Value
HR (beats/min)			
Baseline value	69.7 ± 8.2	75.8 ± 14.0	0.144
1 minutes after intubation	75.5 ± 8.6	92.1 ± 14.5	0.001
2 minutes after intubation	72.4 ± 7.8	87.2 ± 15.7	0.003
3 minutes after intubation	71.2 ± 6.8	82.4 ± 15.4	0.023
Group and time effect			0.014
Time effect			<0.001
Group effect			0.001
MAP (mmHg)			
Baseline value	91.1 ± 6.7	89.4 ± 8.1	0.525
1 minutes after intubation	91.5 ± 15.4	95.2 ± 12.8	0.241
2 minutes after intubation	85.8 ± 13.0	86.6 ± 11.3	0.703
3 minutes after intubation	81.2 ± 11.7	78.9 ± 8.7	0.601
Group and time effect			<0.001
Time effect			0.178
Group effect			0.961

Notes: The baseline values of HR and MAP were the average values measured in three readings of HR and MAP before the dexmedetomidine or saline was administered. Data are presented as mean ± SD.
Abbreviations: HR, heart rate; MAP, mean arterial pressure.

as lidocaine, ketamine, and dexmedetomidine, can be recommended. A recent study suggested that carbonated lidocaine inhalation reduced the EC50 and dose of sufentanil for tracheal intubation in patients with normal weight.[25] In our previous study of obese patients undergoing bariatric surgery, intravenous administration of 1.5 mg/kg lidocaine decreased the EC50 of sufentanil required for tracheal intubation.[26] These results suggested that non-opioid anesthetics could reduce the EC50 and requirement of sufentanil for tracheal intubation. Our current findings further reinforce the potential of dexmedetomidine as a valuable adjunct in opioid-sparing anesthesia protocols, particularly in obese patients.

Table 3 Medications During Anesthesia Induction

Variables	Dexmedetomidine Group	Saline Group	*P*-Value
Propofol dosage (mg)	240.0 (230.0–260.0)	270.0 (250.0–290.0)	0.059
Sufentanil dosage (μg)	12.5 (11.1–15.0)	22.5 (21.5–25.0)	<0.001
Rocuronium dosage (mg)	50.0 (48.8–54.3)	54.0 (50.0–60.0)	0.128

Notes: Data are presented as median (interquartile range).

Table 4 EC50 of Sufentanil and Its 95% CI for the Two Groups

Variables	Dexmedetomidine Group	Saline Group	*P*-Value
EC50 (ng/mL)	0.25	0.43	<0.001
95% CI (ng/mL)	0.17–0.31	0.34–0.46	

Dexmedetomidine is a potent α2 adrenergic receptor agonist that reduces sympathetic outflow, which can lead to hypotension and bradycardia. Therefore, its use may not be appropriate in patients with heart block, hypotension, or severe cardiomyopathy.[27] In our study, two patients were excluded for hypotension. This highlights the necessity of careful patient selection and monitoring when using dexmedetomidine, particularly in populations with potential cardiovascular vulnerabilities. Dexmedetomidine can enhance the role of anesthetics and reduce the dosage of anesthetics required during surgery. Chen et al[28] and Ganesh et al[29] revealed that dexmedetomidine reduced the EC50 of propofol required for I-gel insertion or gastrointestinal endoscopy in non-obese adult patients. Similarly, adjuvant dexmedetomidine reportedly decreased the EC50 of ropivacaine for labor epidural analgesia.[30,31] In another study, dexmedetomidine decreased the EC50 of sevoflurane for supraglottic airway device insertion in morbidly obese patients.[15] These findings suggest that dexmedetomidine can lower the EC50 of several anesthetics. In a response surface model, dexmedetomidine effectively reduced the dose of sufentanil required to inhibit the hemodynamic response caused by tracheal intubation in non-obese patients.[32] In line with these findings, we also found that intravenous dexmedetomidine premedication could decrease the EC50 of sufentanil and sufentanil requirement for tracheal intubation in obese patients. This not only corroborates existing literature but also extends it to a specific population (obese patients) where opioid minimization is particularly beneficial.

The previous work by Al-Metwalli et al[33] in non-obese adult patients showed that the EC50 of sufentanil for successful laryngeal mask insertion was 0.16 ng/mL for anesthesia induction with propofol and sufentanil TCI. This value is lower than the EC50 of sufentanil obtained in our study (0.16 ng/mL vs 0.43 ng/mL). The differences in these findings could be attributed to the differences in the patient selection and methods of the two experiments. In our study, the participants were obese patients, and the Ce of propofol TCI was lower (3.5 μg/mL vs 4.0 μg/mL). In addition, our patients underwent tracheal intubation, which provokes greater stress responses than laryngeal mask insertion, which was performed in the study of Al-Metwalli et al.[33] Therefore, a higher EC50 of sufentanil is needed to inhibit the hemodynamic response caused by tracheal intubation. Jia et al[26] found that when anesthesia was induced by propofol and sufentanil TCI combined with intravenous premedication with 1.5 mg/kg lidocaine in obese patients, the EC50 of sufentanil for tracheal intubation was 0.36 ng/mL, which was higher than reported in the present study (0.36 ng/mL vs 0.25 ng/mL). This may be because dexmedetomidine attenuates the increase in HR after tracheal intubation, thereby enhancing the efficacy of sufentanil in attenuating the hemodynamic response to tracheal intubation. Thus, dexmedetomidine may offer additional benefits over lidocaine in reducing opioid requirements in obese patients.

TCI systems provide stable depth of anesthesia and hemodynamic stability during induction. Previous studies have suggested that TCI of propofol and sufentanil can be successfully used for obese patients.[34,35] In the present study, the dose of propofol in the Marsh pharmacokinetics model was revised as per the adjusted body weight.[36] Besides, the Gepts

pharmacokinetics model was used for sufentanil TCI in obese patients because this model has no relationship with body weight.[35] We selected the dexmedetomidine dosage of 1 μg/kg based on previous data.[37] In general, the anesthesia induction strategies we used in our patients were safe. This approach ensures accurate dosing in obese patients, thereby enhancing the safety and efficacy of anesthesia induction protocols.

This study has several limitations. First, the obese patients were aged between 18 and 49 years, and the findings may not be applicable to other obese patients. Second, we did not measure the concentration of dexmedetomidine during the trail, and thus, it remains unknown whether dexmedetomidine reached its peak concentration during intubation. Third, for dexmedetomidine premedication, only a single dose was given, and understanding whether dexmedetomidine can reduce sufentanil requirement in a dose-dependent manner requires further study. Fourth, this study did not assess the impact of dexmedetomidine on postoperative outcomes like pain and sleep disturbances as the study design focused primarily on the EC50 of sufentanil. Future studies should consider evaluating these potential benefits to provide a comprehensive understanding of dexmedetomidine's role in obese patients.

Conclusion

In summary, intravenous premedication with 1 μg/kg dexmedetomidine decreased the EC50 of sufentanil and sufentanil requirement for tracheal intubation in obese patients. These findings suggest that dexmedetomidine can be effectively used as an opioid-sparing agent in obese patients undergoing surgery. Future research should investigate the dose-dependent effects of dexmedetomidine and assess its impact on postoperative outcomes to further establish its clinical utility in this patient population.

Data Sharing Statement

The data supporting the study findings are available from the corresponding author upon reasonable request.

Ethics Statement

The study was approved by the Institutional Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Approval No. 2024ER198-1).

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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