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ORIGINAL RESEARCH

The Effect of Dezocine on the Median Effective Dose of Sufentanil-Induced Respiratory Depression in Patients Undergoing Spinal Anesthesia Combined with Low-Dose Dexmedetomidine

Yong-Kang Gui[1,2,*], Xiao-Hui Zeng[1,2,*], Rui Xiao[3], Wen-Feng Xi[1–3], Dan Zhang[1–3], Yang Liu[1,2], Si-Hui Zhu[1,2], Xin Da[1,2], De-Wen Shi[1,2], Xu-Dong Hu[1,2], Guang-Hong Xu[1,2]

[1]Department of Anesthesiology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230022, People's Republic of China; [2]Key Laboratory of Anesthesiology and Perioperative Medicine of Anhui Higher Education Institutes, Anhui Medical University, Hefei, Anhui, 230022, People's Republic of China; [3]Department of Anesthesiology, Fuyang Hospital of Anhui Medical University, Fuyang, Anhui, 236113, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guang-Hong Xu, 230032, Tel +86 13856949535, Fax +86 0551 62923704, Email xuguanghong2004@163.com

Purpose: The application of sedation and analgesia in spinal anesthesia has many benefits, but the risk of respiratory depression (RD) caused by opioids cannot be ignored. We aimed to observe the effect of dezocine, a partial agonist of μ-receptor, on the median effective dose (ED50) of sufentanil-induced RD in patients undergoing spinal anesthesia combined with low-dose dexmedetomidine.

Patients and Methods: Sixty-two patients were randomly assigned to dezocine group (DS) and control group (MS). After spinal anesthesia, mask oxygen (5 L/min) and dexmedetomidine (0.1 ug/kg) were given. Five minutes later, patients in the DS group received an Intravenous (IV) bolus of sufentanil and 0.05mg/kg dezocine, while patients in the MS group only received an IV bolus of sufentanil.

Results: ED50 of DS group was 0.342 ug/kg, 95% confidence interval (CI) was (0.269, 0.623) ug/kg, and the ED50 of MS group was 0.291 ug/kg, 95% CI was (0.257, 0.346) ug/kg. There was no difference in the type and treatment measures of RD and hemodynamic changes between the two groups, and no serious adverse reactions occurred in either group.

Conclusion: Dezocine can improve RD induced by sufentanil in patients with spinal anesthesia combined with low-dose dexmedetomidine, and increase the safety window of sufentanil use.

Keywords: spinal anesthesia, respiratory depression, median effective dose, sufentanil, dezocine

Introduction

Spinal anesthesia (SA) is a conventional technique in which a local anesthetic is administered in the cerebrospinal fluid (CSF) within the lumbar spine. This procedure effectively anesthetizes the nerves exiting the spinal cord, resulting in pain relief and subsequent muscle relaxation within the corresponding spinal innervation region. This technique is widely used in obstetrics and gynecology,[1–7] pediatrics,[8,9] orthopedics,[10,11] and urology as well as in various surgical procedures.[12,13] However, as individuals undergoing SA remain conscious throughout the procedure, this can often cause intraoperative anxiety. To address this issue, additional measures involving the use of analgesics and sedatives are warranted.

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Sufentanil, a frequently used fentanyl drug in clinical settings, mainly exerts its effects on μ-receptors.[14] Nevertheless, opioids exert an inherent respiratory depression (RD) effect,[15] and when used improperly, they not induce adequate analgesia and sedation but lead to severe adverse reactions.[16] In China, dezocine is currently the most widely used opioid. It is often administered in conjunction with other opioids to enhance its efficacy or mitigate the occurrence of adverse reactions.[17] Dexmedetomidine, which is a novel selective α-2 adrenergic receptor agonist,[18] can extend the duration of sensory block and delay the time of first remedial analgesia after SA. Therefore, it is frequently used as an adjunctive agent in the field of SA.[19,20]

The 50% effective dose (ED50) of sufentanil to induce RD when administered in a combination with dezocine and dexmedetomidine during SA remains unclear. Previous research has suggested that partial agonists of μ-receptors can mitigate opioid-induced RD.[21,22] Hence, we postulated that dezocine, a partial agonist of μ-receptors, can mitigate sufentanil-induced RD and enhance the ED50 of sufentanil to induce RD when combined with a small dose of dexmedetomidine in patients undergoing SA.

Methods

This study was approved by the Ethics Committee of Fuyang Hospital of Anhui Medical University (KY202206, 2022/07/20), and was registered in the Chinese Clinical Trial Registry before enrollment (registration number: ChiCTR2200063386, 2022/09/05). This study was in full compliance with the Declaration of Helsinki.

Study Participants

The trial was conducted at Fuyang Hospital of Anhui Medical University from October 2022 to March 2023. Sixty patients, aged 18–60 years, American Society of Anesthesiologists (ASA) physical status I–II, body mass index (BMI) 18.5–27 kg/m2, scheduled for SA were enrolled in this study. Patients with long-term use of psychotropic drugs, a history of alcohol abuse, heart, lung, liver, kidney, neurological dysfunction, and severe drug allergy were not included. Patients with unsatisfactory spinal anesthesia level, severe adverse reactions, and incomplete records of the Case Report Form (CRF) were excluded.

Written informed consent was obtained from all patients participating in this experiment.

Randomization and Blinding

Patients were randomly assigned to the dezocine (DS) and control (MS) groups using the random number table method. The numbers were placed inside opaque envelopes, which were opened by the anesthesiologist once the patient entered the operating room and the drugs was prepared according to the numbers in the envelope.

To ensure unbiased evaluation, an investigator who was blinded to the group assignments performed respiratory monitoring for 10 min. This approach helped minimize potential observer bias.

Furthermore, all SA procedures in this study were performed by the same experienced anesthesiologist to ensure uniformity and reduce the impact of interoperator variability on the results.

Anesthesia Procedure

Blood pressure (BP), electrocardiogram, pulse oxygen saturation (SpO2), and end-tidal carbon dioxide partial pressure (PETCO2) were monitored on admission. Subarachnoid puncture was performed at the lumbar 2/3 interspace (L2/3) in the left lateral position. CSF reflux indicated a successful puncture. Next, 2 ml of 0.5% ropivacaine was injected within 10s and the sensory level was controlled in the supine position to the plane of the tenth thoracic vertebra (T10). After the plane was fixed, mask oxygen inhalation was administered at 5 L/min. The DS group was administered dexmedetomidine (0.1 μg/kg) for 5 min, followed by dezocine (0.05 mg/kg) and sufentanil. Conversely, the MS group received dexmedetomidine (0.1 μg/kg) for 5 min, followed by sufentanil. The dose of sufentanil was determined using the Dixon up–down method and the occurrence of RD. Based on the preliminary experiment, the first dose of sufentanil was selected (0.3 and 0.245 μg/kg in the DS and MS groups, respectively). The adjacent dose ratio was 1.1. If the patient exhibited RD within a span of 10 min after sufentanil infusion, the dose for the next patient was reduced by one level;

otherwise, it was increased by one level. The experiment was terminated when there were seven crossovers of positive to negative alteration.

Criteria for Respiratory Depression

RD was diagnosed if one or more of the following conditions were observed: respiratory rate (RR) ≤ 8 times/min, apnea ≥ 15s, SpO2 ≤ 90%, PETCO2 ≥ 55 mmHg, arterial PaCO2 (partial pressure of carbon dioxide) ≥ 55 mmHg, and complaints of dyspnea.[23]

Management Measures After Respiratory Depression and Significant Hemodynamic Changes

When a patient experienced RD, the following treatments were gradually provided in the mentioned order until the resolution of RD or hypoxia symptoms: 1) increased oxygen flow (5 L/min), 2) language and physical stimulation, 3) lifting of the jaw, 4) mask-assisted ventilation, and 5) artificial airway implantation (laryngeal mask/tracheal intubation).

When the patient's heart rate (HR) was <50 beats per minute and blood pressure (BP) was >30% of the baseline value, intravenous atropine and ephedrine were administered, respectively.

Observing Indicators

The primary outcome of this study was the ED50 of sufentanil in the two groups at the end of the study. The secondary outcomes were the dose of ropivacaine, level of anesthesia, Ramsay score, vital signs (such as BP, HR, RR, SpO2, and PETCO2), and incidence of adverse reactions (SA-related complications, HR and BP drop, dizziness, headache, nausea, vomiting, etc.) recorded during the trial.

Statistical Analysis

Based on the methods used by Wu and Oh TK et al,[24,25] and a previous study involving 13 subjects, we determined that the mean dose of sufentanil required to induce RD in patients undergoing SA was 0.291 μg/kg (SD= 0.0495), when not combined with dezocine. We believe that a 10% sufentanil dose difference between the two groups indicates that the use of dezocine is meaningful for the antagonistic potency of sufentanil-induced RD. Assume a type I error of 0.05 (Alpha= 0.05) and a power of 0.9 (1-Beta= 0.9). Considering a dropout rate of 20%, we aimed to enroll 31 patients in each group.

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) V26.0. The normality of distribution was assessed using the Shapiro–Wilk test. Patient's characteristics were compared between the two groups using the independent-sample *t*-test for continuous variables with normal distribution and the Mann–Whitney *U*-test for those with nonnormal distribution. For categorical variables, Pearson's χ^2 test was used as appropriate.

Hemodynamic indices were tested via repeated measures analysis of variance. Normally distributed and skewed data were expressed as mean ± standard deviation and median (interquartile range), respectively. Count data were tested using the chi-squared test. The significance level for all statistical tests was set at $P \leq 0.05$.

Results

A total of 62 eligible patients who provided written informed consent were evaluated. They were sequentially selected until seven crossovers were attained. One patient in the MS group and another in the DS group were excluded because of unsatisfactory block plane and incomplete experimental data recording, respectively. Thus, 51 patients (DS group, 24; MS group, 27) were included in the final analysis. (Figures 1-3). All SA procedures in this study were successfully performed by one same experienced anesthesiologist.

As shown in Table 1, the demographic characteristics of the two groups of patients were similar. The gender composition and the level of spinal anesthesia were similar between the two groups. Ramsay scores were similar in both groups. No significant difference was observed in the doses of dexmedetomidine and ropivacaine in the two groups.

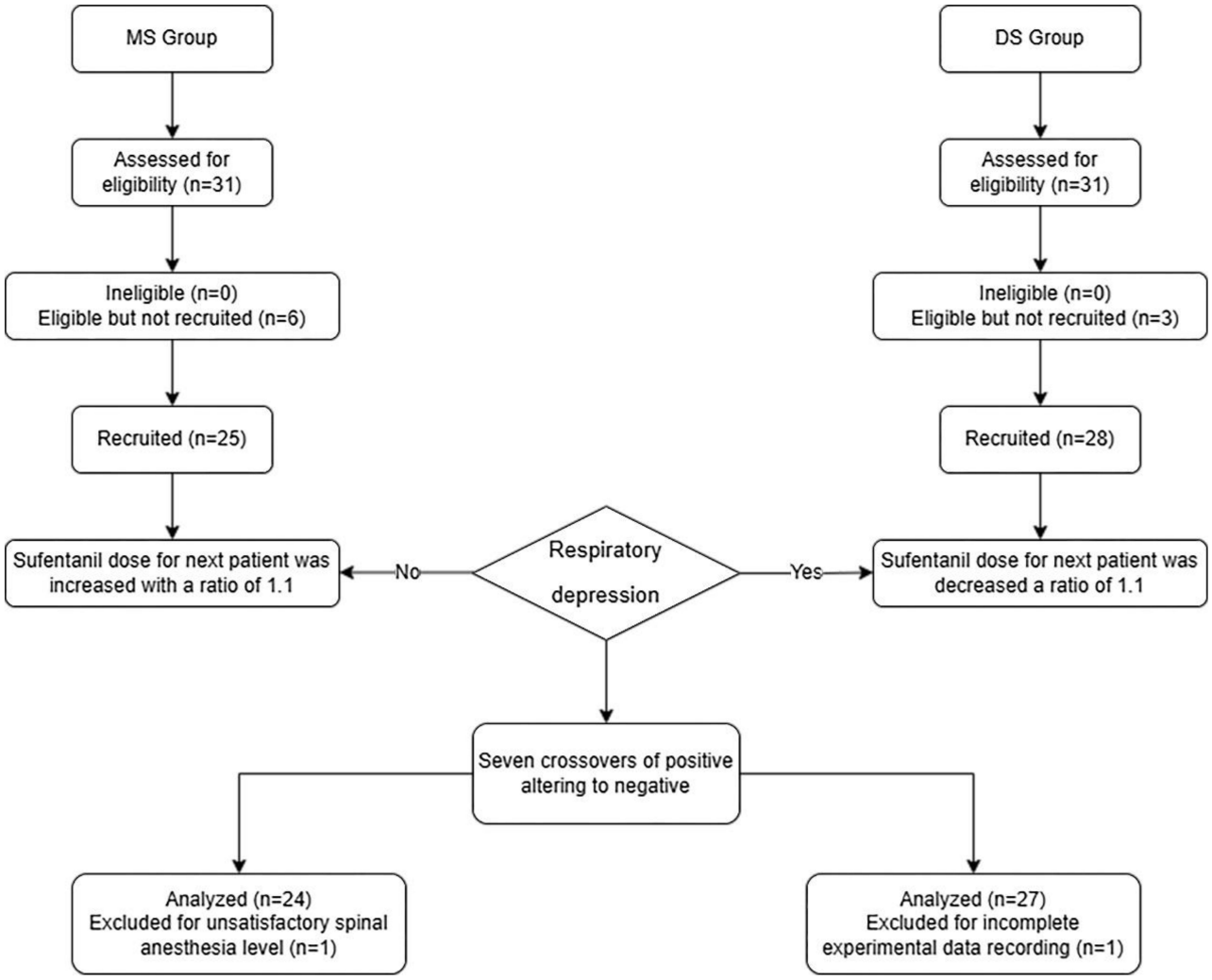

Figure 1 Flow diagram for the Dixon up-and-down method.
Abbreviations: DS, dezocine group; MS, control group; positive, presence of respiratory depression; negative, absence of respiratory depression.

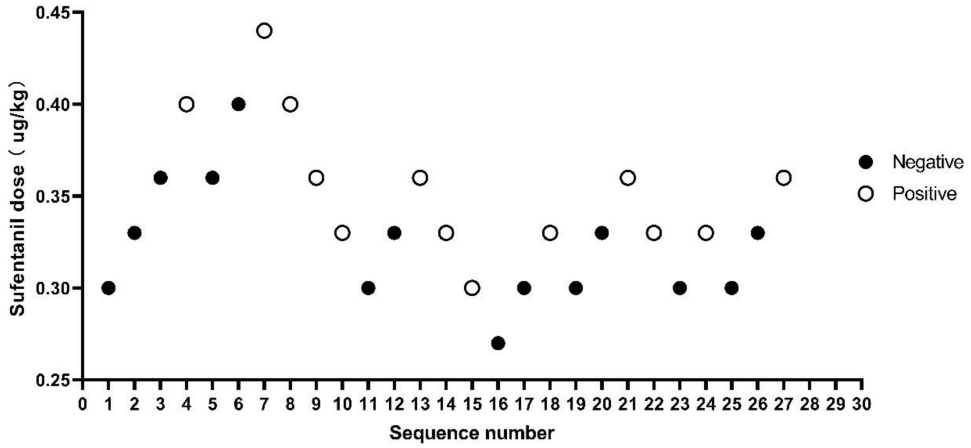

Figure 2 Response in DS Group.
Abbreviations: DS, dezocine group; positive, presence of respiratory depression; negative, absence of respiratory depression.

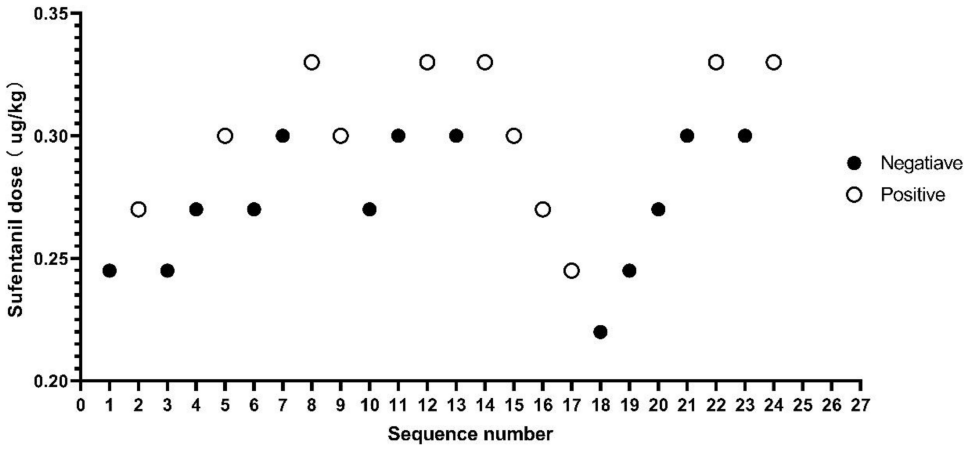

Figure 3 Response in MS Group.
Abbreviations: MS, control group; positive, presence of respiratory depression; negative, absence of respiratory depression.

Using the Dixon up–down method,[26,27] the ED50 values in the DS and MS groups were found to be 0.342 μg/kg (95% confidence interval [CI], 0.269–0.623) and 0.291 μg/kg (95% CI, 0.257–0.346), respectively. (Figure 4).

No significant difference was observed in the occurrence and treatment of RD, hemodynamic changes, and incidence of adverse reactions between the two groups the during the experimental observation period. (Tables 1–4).

Discussion

SA is widely used in various surgeries. Patients undergoing SA remain conscious throughout the operation, which results in certain drawbacks such as needle-related apprehension and recollection of the surgical process.[28,29] These are important sources of fear and anxiety for the patients,[30] further highlighting the importance of sedation. An appropriate sedation can provide analgesia and amnesia as well as relieve anxiety and fear. Sedation can improve patient's satisfaction with regional anesthesia and increase patient acceptance of the associated techniques.[31] Consequently, the use of appropriate sedation and analgesia techniques can significantly improve the comfort of patients when undergoing SA, effectively alleviating their anxiety and fear.

Dezocine is the most extensively used opioid in China, accounting for 44% of the national opioid analgesic market.[32] It has weaker RD effects than commonly used μ-receptor agonists, such as fentanyl. Furthermore, it exerts a "capping effect".[17,33–35] The receptor profile of dezocine differs from that of known pure μ-agonists; therefore, it is allowed to be

Table 1 Drugs and Social Demographic Variable of Participants

Variable	MS Group	DS Group	P
Age	40.42±9.33	42.37±8.10	0.427
Height	163.0 (158.0, 168.0)	164.0 (160.0, 167.0)	0.977
Weight	62.21±8.67	62.19±8.03	0.992
BMI	22.71±2.46	23.06±2.041	0.577
Sex (Male/Female)	6/18	5/22	0.574
Sensory plane (T10/T12)	21/3	22/5	0.553
Ropivacaine	2.50 (2.50, 2.50)	2.50 (2.50, 2.50)	>0.999
Dexmedetomidine	6.22±0.87	6.22±0.80	0.992
Sufentanil	18.02±3.56	21.04±3.40	0.003
ED50	0.342	0.291	
95% CI	(0.269, 0.623)	(0.257, 0.346)	
Adverse reactions	0	0	

Notes: Values are expressed as mean ± SD, median (IQR), frequency (%), or number.
Abbreviations: DS, dezocine group; MS, control group; BMI, body mass index; ED50, Median effective dose; 95% CI, 95% confidence interval (CI).

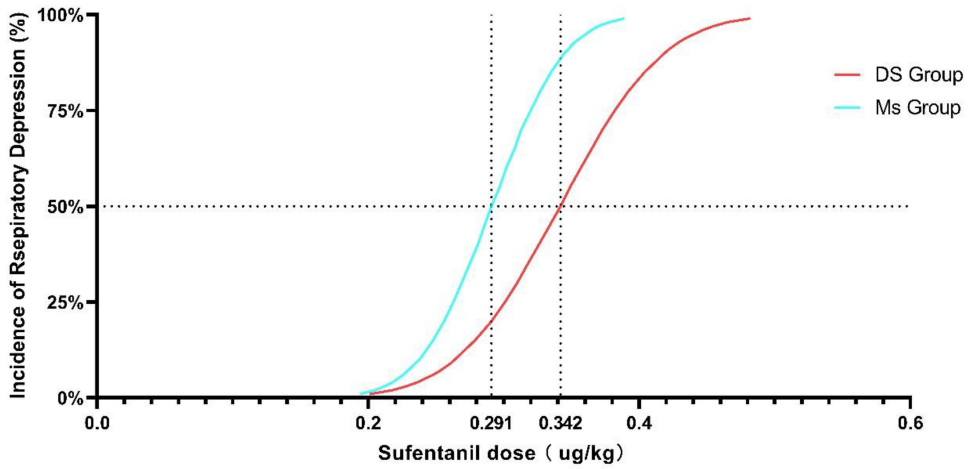

Figure 4 Dose-effect curve. According to the results of DIXON's up-and-down method, the dose-effect curve of sufentanil induced respiratory depression was drawn to predict the adverse reactions of the two groups.
Abbreviations: DS, dezocine group; MS, control group.

used in a combination with other opioids to improve efficacy or reduce the occurrence of adverse effects.[17] For example, dezocine can reduce the incidence of postoperative delirium when used during the induction of anesthesia[36] and exert therapeutic effects on depression.[37,38]

Buprenorphine, a partial agonist of opioid receptors,[39] can reverse opioid-induced RD in humans and animals.[40,41] Because dezocine is also a partial agonist of μ-receptors, we used it in combination with sufentanil and concluded that dezocine could partially antagonize sufentanil-induced RD in SA. This effect may be attributed to the role of dezocine as

Table 2 The Types of Respiratory Depression

Types of Respiratory Depression	DS Group	MS Group	*P*
1	8 (61.5%)	6 (54.5%)	0.463
1.2	1 (7.7%)	3 (27.3%)	
1.2.4	2 (15.4%)	0 (0%)	
1.2.5	1 (7.7%)	2 (18.2%)	
1.2.3.5	1 (7.7%)	0 (0.0%)	
Total	13	11	

Notes: Types of Respiratory depression: 1. Respiratory rate (RR) ≤8 times/min; 2. Apnea ≥15s; 3. SpO2 ≤90%, PETCO2 ≥55 mmHg; 4. Arterial blood gas analysis arterial partial pressure of carbon dioxide (PaCO2) ≥55 mmHg; 5. Patients subjectively reported dyspnea.
Abbreviations: DS, dezocine group; MS, control group.

Table 3 The Management Measures of Respiratory Depression

Management Measures of Respiratory Depression	DS Group	MS Group	*P*
1	3 (23.1%)	2 (18.2%)	>0.999
1,2	9 (69.2%)	9 (91.8%)	
1,2,3	1 (7.7%)	0 (0.0%)	
Total	13	11	

Notes: The management measures of respiratory depression: 1. Increase oxygen flow (5L/min); 2. Language and physical stimulation; 3. Lift the jaw; 4. Mask assisted ventilation; 5. Artificial airway implantation (laryngeal mask/tracheal intubation).
Abbreviations: DS, dezocine group; MS, control group.

Table 4 Hemodynamic Measures

Variable	MS Group	DS Group	*P*
SBP before injection	126.00±17.98	128.52±17.73	0.682
SBP 1 min after injection	125.17±19.85	127.48±20.33	
SBP 2 min after injection	122.00±18.47	126.07±20.22	
SBP 3 min after injection	121.01±18.84	123.33±20.49	
SBP 4 min after injection	122.13±19.38	125.56±19.74	
SBP 5 min after injection	123.13±18.87	124.89±22.35	
SBP 6 min after injection	122.25±17.32	124.73±18.21	
SBP 7 min after injection	124.29±18.12	127.70±18.39	
SBP 8 min after injection	125.63±19.41	125.67±17.64	
SBP 9 min after injection	126.21±18.49	128.44±19.63	
SBP 10 min after injection	126.13±21.75	126.19±18.72	
DBP before injection	69.63±11.29	76.07±11.77	0.195
DBP 1 min after injection	72.00±12.15	73.85±11.90	
DBP 2 min after injection	68.83±11.14	72.33±13.61	
DBP 3 min after injection	69.71±12.53	71.3±11.29	
DBP 4 min after injection	69.37±13.99	72.52±10.75	
DBP 5 min after injection	69.54±11.75	72.33±11.58	
DBP 6 min after injection	69.92±11.93	72.41±10.21	
DBP 7 min after injection	70.21±11.60	73.48±11.14	
DBP 8 min after injection	70.25±11.89	71.63±9.69	
DBP 9 min after injection	69.63±9.65	71.78±11.39	
DBP 10 min after injection	70.42±10.91	72.33±12.13	
HR before injection	72.00±10.14	69.85±11.10	0.48
HR 1min after injection	66.87±12.41	64.41±11.56	
HR 2 min after injection	65.33±11.18	63.01±10.59	
HR 3 min after injection	64.92±11.07	62.93±10.89	
HR 4 min after injection	65.08±10.71	64.26±11.59	
HR 5 min after injection	66.71±10.47	65.37±11.08	
HR 6 min after injection	68.42±10.99	64.37±9.46	
HR 7 min after injection	68.08±11.18	64.78±8.10	
HR 8 min after injection	69.19±9.89	65.19±8.96	
HR 9 min after injection	68.83±10.54	67.00±10.16	
HR 10 min after injection	69.29±10.11	66.48±10.73	

Abbreviations: DS, dezocine group; MS, control group; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

a partial agonist of μ-receptors, where it may block or displace the binding of pure opioid receptor agonist to the μ-receptor when combined with dezocine. This mechanism is similar to that observed in a previous study and provides a plausible explanation for the observed increase in the ED50 in the DS group.[17]

The dose–response curve of a drug is usually S-shaped. The median ED50 is located at the midpoint of the curve, which indicates the dose that produces a positive response for 50% of individuals. Thus, it is often used as an index to reflect the potency of drug action.[42]

The difference in ED50 and amount of sufentanil used between the groups in this trial also confirmed that dezocine can decrease the ED50 of sufentanil-induced RD in patients undergoing SA. The implications of this finding within the field of SA are profound, as it demonstrates the potential of the combined use of sufentanil and dezocine to simultaneously minimize the incidence of RD while providing adequate sedation and analgesia. This undoubtedly expands the safety threshold of sufentanil administration during SA.

All patients with RD exhibited decreased RR, and similar observation was reported by Smart et al,[43] and suggests that respiratory cycle monitoring can be used as a sensitive indicator of sufentanil-induced RD. suggesting that respiratory cycle monitoring can be used as a sensitive indicator of sufentanil-induced RD. When RD occurs, increased inspired

oxygen concentration and speech stimulation could effectively improve the ventilation of patients. Similar to previous studies,[44,45] only one patient in this study required jaw lifting to maintain satisfactory ventilation after the above treatments, but none required artificial airway implantation.

This study has several limitations. First, the results only apply to patients undergoing SA and are not a reference for the ED50 of sufentanil to induce RD under the same drug combination in patients in whom other anesthesia techniques are used. Second, this study was majorly conducted in the Han and Yellow race, and further experiments may be warranted to explore the ED50 of sufentanil under similar clinical conditions in other ethnic groups and races.

Conclusion

In conclusion, the use of dezocine can increase the ED50 of sufentanil to induce RD in patients undergoing SA combined with low-dose dexmedetomidine. This may be related to the competitive inhibition of μ-receptors by dezocine.

Data Sharing Statement

Under reasonable requirements, the data and material of this study can be obtained from the corresponding author. The data are not publicly available due to privacy restrictions.

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Disclosure

The authors declare no conflicts of interest in this work.

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