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CLINICAL TRIAL REPORT

Effect of Dexmedetomidine on the ED_{50} and ED_{95} of Sufentanil in Patient-Controlled Intravenous Analgesia After Cesarean Section: A Randomized, Controlled, Double-Blind Trial

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Purpose: To determine the effect of dexmedetomidine on the ED_{50} and ED_{95} of sufentanil in patient-controlled intravenous analgesia (PCIA) after cesarean section.

Patients and Methods: Parturients who underwent elective cesarean section (n = 80) were randomly assigned to either the sufentanil group (S group) or the dexmedetomidine-sufentanil combination group (DS group). Patients in the S group received a combination of sufentanil, 5 mg of tropisetron, and saline, whereas patients in the DS group were administered 1.5μg/kg of dexmedetomidine in addition to sufentanil, 5 mg of tropisetron, and saline. The ED_{50} and ED_{95} of sufentanil were determined by Dixon sequential method. We used probit regression to calculate the ED_{50}, ED_{95}, and 95% confidence intervals for sufentanil in each group.

Results: The ED_{50} and ED_{95} for sufentanil in the S group were 1.634 (95% CI: 1.476–1.810)μg/kg and 2.035 (95% CI: 1.841–3.312) μg/kg, respectively. The ED_{50} and ED_{95} for sufentanil in the DS group were 1.275 (95% CI: 1.187–1.353)μg/kg and 1.503 (95% CI: 1.406–1.824)μg/kg. The VAS scores with rest at t_5 and with movement at t_4- t_5 were lower in the DS group ($P< 0.05$). The t_2-t_5 Ramsay scores in the DS group were higher than those in the S group ($P< 0.05$). The doses of sufentanil and tramadol were markedly reduced in the DS group, while the onset of first lactation occurred significantly earlier in the DS group ($P< 0.05$). Compared with the S group, the DS group had a lower incidence of nausea, vomiting, and skin itching ($P< 0.05$), and lower frequency of patient-controlled analgesia (PCA) episodes ($P< 0.05$), and better postoperative pain satisfaction ($P< 0.05$).

Conclusion: The 1.5μg/kg dexmedetomidine can significantly decrease the ED_{50} and ED_{95} of sufentanil in patient-controlled intravenous analgesia after cesarean section, provide good postoperative analgesia and sedation, and promote the earlier occurrence of first lactation.

Keywords: dexmedetomidine, sufentanil, cesarean section, postoperative analgesia, ED_{50}, ED_{95}

Introduction

Parturients often experience moderate-to-severe pain following a cesarean section, which can lead to anxiety and insomnia, impact early bonding between the parturient and the baby, impede postoperative recovery, and even elevate the risk of developing chronic pain and postpartum depression.[1] Currently, there are different ways of analgesia after cesarean section in different geographical areas. In North America and Europe, neuraxial long-acting opioids (morphine, dihydromorphine, and hydromorphone) are the most common form of analgesia.[2] However, patient- controlled intravenous analgesia with opioids is the most commonly used method in China.[3] Because PCIA allows patients to control the dose of drugs according to their own needs, the optimal analgesic effect can be achieved with the least dose of drugs.[4] Sufentanil is a highly selective μ-receptor agonist with the characteristics of fast-acting, short half-life, and strong

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analgesic effect, which makes it an ideal PCIA drug. The reduction of opioids in PCIA can attenuate postoperative side effects.[5] Dexmedetomidine is a highly selective α-2 receptor agonist with sedative, hypnotic, analgesic, and antisympathetic effects without respiratory depression. Administering dexmedetomidine in conjunction with sufentanil in PCIA for postoperative pain relief following cesarean section markedly enhanced analgesia efficacy, minimized the dosage of sufentanil, and simultaneously reduced the occurrence of nausea and vomiting.[6] We hypothesized that dexmedetomidine can significantly decrease the ED_{50} and ED_{95} of sufentanil in PCIA after cesarean section. At present, there is no clinical study to investigate the effect of dexmedetomidine on the ED_{50} and ED_{95} of sufentanil in PCIA after cesarean section. Therefore, we conducted this clinical trial to study the effect of dexmedetomidine on the ED_{50} and ED_{95} of sufentanil in PCIA after cesarean section using the sequential method.

Materials and Methods

Ethical Statement

The present study was approved by the Ethics Committee of The Second Clinical Medical College of North Sichuan Medical College (Review No. 122, 2020) and registered in the Chinese Clinical Trials Registry on 23/12/2020 (Registration Number: ChiCTR2000041302). Pregnant women who underwent elective cesarean section in our hospital from January 2021 to May 2021 were enrolled in this prospective randomized, controlled, double-blind study. All patients and their families provided informed consent before the trial. All procedures followed the applicable CONSORT 2010 guidelines. Our research complies with the Declaration of Helsinki.[7]

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) women who were 20–42 years old; (2) individuals with American Society of Anesthesiologists (ASA) physical status II; (3) single primigravidas with 37–40 weeks of gestation; (4) parturients who opted for postoperative intravenous analgesia; (5) parturients who agreed to breastfeed.

The exclusion criteria were as follows:(1) contraindications for intraspinal anesthesia (coagulation abnormalities, spinal deformity, and a history of spinal surgery, etc); (2) allergic to α-2 adrenergic agonists or opioids; (3) patients with bradycardia (heart rate less than 60 beats/min) and atrioventricular conduction block; (4) Recently administered sedatives or opioids; (5) Failed spinal anesthesia; (6) Those who could not understand VAS or Ramsay scores, or could not use a PCA pump correctly; (7) Those who participated in other clinical trials.

The exit criteria were as follows: (1) parturients with intraoperative and postoperative massive bleeding (> 800 mL); (2) Parturients who required sedatives and analgesics during the operation; (3) Parturients who requested to discontinue the use of the PCA pump.

Randomization and Blind Method

Parturients were randomly divided into S and DS groups according to a computer-generated random sequence. The random assignment numbers were written on the cards and sealed in an opaque envelope. At the end of the cesarean section, the anesthesia nurse, who was not involved in the study, prepared the intravenous analgesia pump according to the concealed information in the envelope for random allocation. After surgery, the anesthesia nurse handed over the PCA pump to the follow-up anesthesiologist for this trial. After the completion of this trial, the follow-up anesthesiologist gave the data to the statistician, who calculated the dose of sufentanil for the next parturients in the group based on whether the analgesia was effective or ineffective, and then informed the anesthesia nurse. This process continued for subsequent participants until the end of the trial. Follow-up anesthesiologist, statisticians, participants, obstetrician, and obstetric ward staff were unaware of the grouping.

Sequential Trial

Based on the pre-experiment results, the first patient in each group was given 1.5 μg/kg of sufentanil for postoperative analgesia. Within 6 hours after surgery, VAS score≤3 was considered effective analgesia. Otherwise, it was ineffective. Furthermore, the dose ratio of Sufentanil administered to the adjacent maternal subjects within the study sequence was

1:1.1.[8] For patients who experienced ineffective analgesia, the subsequent dose of sufentanil used for maternal postoperative analgesia in the group was adjusted upwards to 1.1 times the previous dosage. Conversely, if the analgesia was effective, the subsequent dose of sufentanil was adjusted downward by dividing the previous dosage by 1.1. The primary endpoint of this test was marked by the presence of at least six inflection points in the sequential test.[9]

Anesthesia Process

We informed the participants of the preoperative precautions and the risks of anesthesia, obtained the signature of each participant on the informed consent form, introduced the VAS and Ramsay scoring systems to the participants and their families, and taught the participants to use the PCA pump correctly the day before the operation.

The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), peripheral oxygen saturation (SpO_2), and electrocardiography (ECG) were routinely monitored after the parturient entered the operating room. The parturient inhaled 3–5 L/min of oxygen through a face mask. The Lactated Ringer's solution (6–8 mL/kg) was quickly administered intravenously before spinal anesthesia, and the intravenous fluids were adjusted for fluid maintenance requirements during cesarean section. The anesthesiologist placed the parturient in a left lateral position and punctured the L3-4 spinal space with a disposable lumbar puncture needle. After confirming that the subarachnoid puncture was successful, 2mL of 0.75% bupivacaine was diluted to 3mL with cerebrospinal fluid, and then, 9–12 mg of 0.5% bupivacaine was slowly injected according to the height of the individual. Next, position the patient flat on the bed and tilt the operating table 15 degrees to the left. The blocked dermatomes were determined using the needle prick method. The surgery commenced once complete sensory blockade was established at T_4-T_6 dermatomes. The parturient was transferred to the Post-Anesthesia Care Unit (PACU) after the surgery. When the blocked dermatomes decreased below T_8, the follow-up anesthesiologist performed postoperative analgesia for the patient by using the PCIA pump. The formula of PCIA in the S group consisted of sufentanil and tropisetron 5mg, whereas in the DS group, it included sufentanil, tropisetron 5mg, plus 1.5μg/kg of dexmedetomidine. The total volume of the PCIA pump in both groups was 120mL, with a loading dose of 2mL, a maintenance dose of 2 mL/h, an additional quantity of 0.5mL, and a locking time of 15 minutes for both groups. When the HR of the parturient was below 50 beats/min, 0.5 mg of intravenous atropine was administered until the HR was greater than 60 beats/min. When the SBP of the parturient was below 90 mmHg or decreased by more than 20% of the basal value of the blood pressure, 0.05 mg of phenylephrine was administered intravenously. If parturients vomited, 5 mg of tropisetron was injected intravenously. When the parturient experienced respiratory depression, inhaled oxygen was administered and/or naloxone was injected intravenously. If the VAS score remained above 3 despite the use of PCA, 2 mg/kg of tramadol was administered intramuscularly for pain relief.[4]

Data Collection

The primary outcome was the ED_{50}, ED_{95}, and 95% CI of sufentanil in patient-controlled intravenous analgesia after cesarean section.

The secondary outcomes were as follows:

1. The HR, SBP, DBP, and SpO_2 were recorded 5min before anesthesia (t_0), 2 hours (t_1), 4 hours (t_2), 6 hours (t_3), 8 hours (t_4), 24 hours (t_5), and 48 hours (t_6) after surgery.
2. The VAS scores and the Ramsay scores were recorded 4 hours (t_2), 6 hours (t_3), 8 hours (t_4), 24 hours (t_5), and 48 hours (t_6) after surgery.
3. The dosages of sufentanil and tramadol and the number of PCA were recorded.
4. The time of the first lactation was recorded by lactation consultants, who conducted one follow-up visit per day. Additionally, the mother self-reported this time.
5. Information on hypotension, bradycardia, dizziness, nausea, vomiting, skin itching, and the satisfaction of parturients with postoperative analgesia was recorded. General information, such as age, weight, height, gestational week, and surgery time was recorded for both groups.

Postoperative pain intensity was evaluated using a 10-cm visual analogue scale (VAS) with the left end of the line marked as 0 (painlessness), and the right end marked as 10 (severe pain). Scores were interpreted as follows: 0 = no pain, 1–3 = mild pain, 4–6 = moderate pain, 7–10 = severe pain.[10]

Ramsay score: 1 = agitated or anxious, 2 = calm, cooperative, and has directional power, 3 = fell asleep but could follow instructions, 4 = sleepy, responded quickly to shouting, 5 = lethargic, responded slowly to shouting, and 6 = lethargic and did not respond to stimulation.1 = shallow sedation, 2–4 = satisfactory sedation, 5–6 = excessive sedation.[11]

Sample Size

The non-independence of data and the unknown distribution in studies using the up-and-down sequential methods hindered the calculation of sample sizes.[9] Simulation studies have demonstrated that 20 to 40 patients per group are required. In our study, each group consisted of 35 patients, which was sufficient for statistical analyses.[12]

Statistical Analysis

All data in this study were analyzed using the SPSS22.0 (SPSS Inc., Chicago, IL) statistical software. The Shapiro–Wilk test was employed to ascertain whether the data followed a normal distribution pattern. Quantitative data that followed a normal distribution were expressed as Mean ± Standard Deviation (Mean ± SD). The differences between groups were determined through the conduct of *t*-tests, while differences across various time points were evaluated using analysis of variance (ANOVA) for repeated measurement data. Quantitative data that did not follow a normal distribution were expressed as the median and interquartile range (IQR) and analyzed using Mann–Whitney *U*-tests. Categorical data were presented in the format of n (%) and subjected to chi-square testing for analysis. The ED_{50}, ED_{95}, and 95% confidence intervals for both groups were calculated using the probit method. The differences were considered to be statistically significant at $P< 0.05$.

Results

A total of 80 pregnant women were recruited and screened, among whom 2 had spinal deformities, and 2 were taking sedative medication due to hypertensive disorders complicating pregnancy. Finally, a total of 76 pregnant women were randomly assigned to the S and DS groups. One pregnant woman failed spinal anesthesia and two were lost to follow-up in the S group. Two pregnant women failed spinal anesthesia and one was lost to follow-up in the DS group. Finally, 35 pregnant women in each group were included in the statistical analysis. All mothers underwent surgery approximately at 9:00 a.m. All procedures followed the applicable CONSORT guidelines (Figure 1). The two groups showed no significant differences in age, weight, height, gestational week, and surgery time ($P> 0.05$) (Table 1).

The distribution sequence of participants and their responses to different doses of sufentanil in the S group are shown in Figure 2A, while those in the DS group are presented in Figure 2B. The ED_{50} and ED_{95} of sufentanil in the S group were 1.634 (95% CI: 1.476–1.810)μg/kg and 2.035 (95% CI: 1.841–3.312)μg/kg, respectively. The ED_{50} and ED_{95} of sufentanil in the DS group were 1.275 (95% CI: 1.187–1.353)μg/kg and 1.503 (95% CI: 1.406–1.824)μg/kg. The dose-effect curves for participants in the S group are presented in Figure 3A, while those for participants in the DS group are shown in Figure 3B.

No significant differences were recorded in HR, SBP, DBP, and SpO_2 between the groups ($P > 0.05$), as shown in Figures 4–6.

The VAS scores at rest and during movement at different time points in the two groups are shown in Table 2. Compared to t2, VAS scores in the S group at rest (t4-t6) and during movement (t6), as well as VAS scores in the DS group at rest and during movement (t4-t6), decreased more significantly ($P < 0.05$). The VAS scores during movement at $t_{4\text{-}5}$ and during rest at t_5 were significantly lower in the DS group compared to the S group ($P< 0.05$). The Ramsay scores at different time points in the two groups are shown in Table 3. The Ramsay scores from t_2 to t_5 increased more significantly in the DS group than in the S group ($P< 0.05$).

The comparison of maternal sufentanil and tramadol dosage, number of PCA requests, and time to first lactation between the two groups is presented in Table 4. The doses of sufentanil and tramadol were significantly lower in the DS

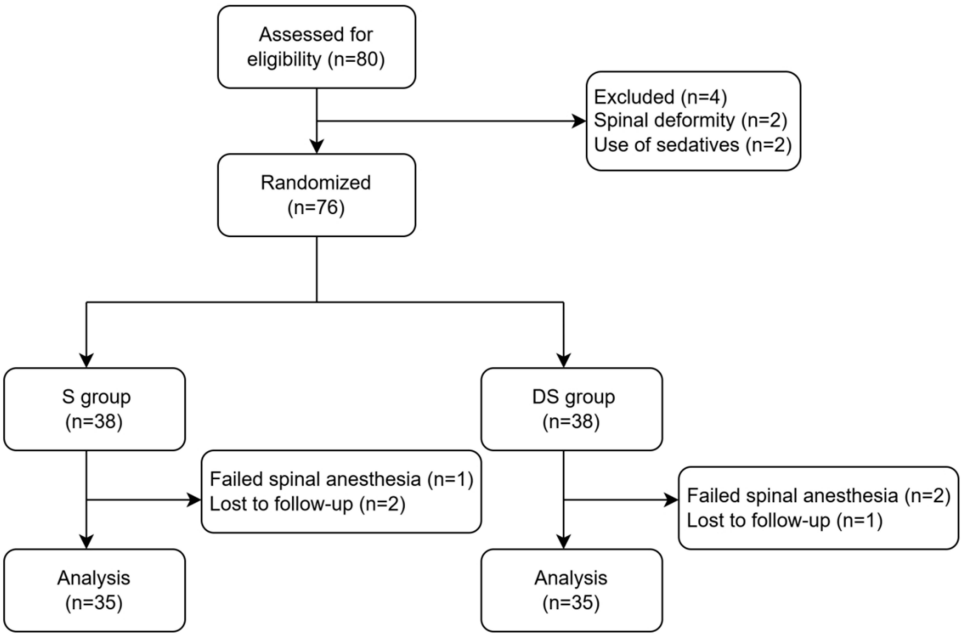

Figure 1 A flowchart of the study.

group than in the S group ($P< 0.05$). The number of PCA in the DS group was significantly less than in the S group ($P< 0.05$). The first lactation time after the operation was earlier in the DS group than in the S group ($P< 0.05$).

The adverse reactions and satisfaction with postoperative analgesia between the S and DS groups are shown in Table 5. There was no significant difference in adverse reactions such as hypotension, bradycardia, and dizziness between the two groups ($P>0.05$). The incidences of nausea, vomiting, and skin pruritus were significantly lower in the DS group compared to the S group ($P<0.05$). The satisfaction of postoperative analgesia in the DS group was higher than that in the S group ($P<0.05$).

Discussion

In this study, we found that 1.5 μg/kg dexmedetomidine decreased the ED_{50} of sufentanil from 1.634 (95% CI: 1.476–1.810)μg/kg to 1.275 (95% CI: 1.187–1.353)μg/kg, and ED_{95} of sufentanil from 2.035 (95% CI: 1.841–3.312) μg/kg to 1.503 (95% CI: 1.406–1.824)μg/kg in PCIA patients after cesarean section. It reduced postoperative pain scores, the frequency of PCA administration, and the doses of sufentanil and tramadol required, provided suitable postoperative sedation, shortened the time to first breastfeeding, and decreased the incidences of nausea, vomiting, and skin itching. The administration of dexmedetomidine significantly improved satisfaction with postoperative analgesia, and had no effect on maternal hemodynamics.

Table 1 Characteristics of the Participants in the S and DS Groups

Index	S Group (n = 35)	DS Group (n = 35)	F values	P values
Age (yr)	27.2 ±4.8	26.4 ±4.2	0.480	0.491
Weight (kg)	67.6 ±4.7	65.5 ±5.2	3.198	0.078
Height (cm)	158.1 ±7.0	157.6 ±8.5	0.084	0.772
Gestational week (wk)	39.0 ±1.1	39.2 ±1.3	0.353	0.554
Surgery time (min)	64.4 ±5.9	66.4 ±4.6	2.483	0.120

Note: Values are mean ± SD.
Abbreviations: SD, standard deviation; yr, year; wk, week.

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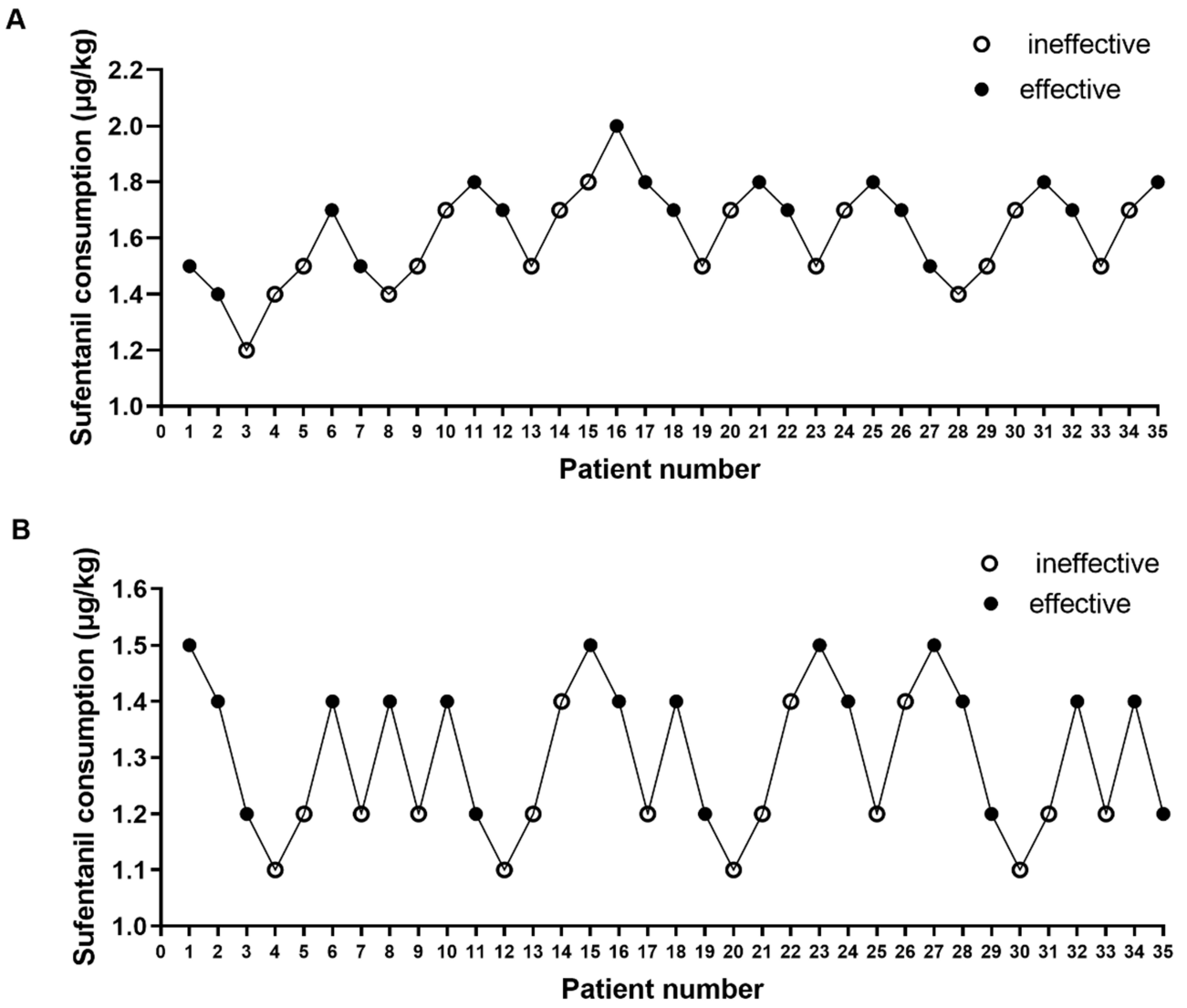

Figure 2 The distribution sequence and response of the patients to different doses of sufentanil in the two groups. (**A**) represents the S group, and (**B**) represents the DS group.

We used the sequential method to determine the effect of dexmedetomidine on the ED_{50}, ED_{95} of sufentanil in PCIA during cesarean section. Our study found that, compared to the S group, the ED_{50} of sufentanil in patients in the DS group decreased by 22%, and the ED_{95} decreased by 26%. Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist with sedative, analgesic, hypnotic, and anxiolytic effects. Dexmedetomidine can provide analgesic effects by (1) inhibiting the norepinephrine pathway to promote inhibitory postsynaptic potentials in the spinal cord, (2) inhibiting the locus coeruleus, which may lead to sedation, and (3) activating α-2 epinephrine receptor on spinal glial neurons that induce outward potassium currents, which hyperpolarize pain-producing cells to relieve pain.[13] We speculate that dexmedetomidine's inherent analgesic effect reduces the ED_{50} and ED_{95} of sufentanil in PCIA after cesarean section.

Dexmedetomidine, when combined with sufentanil, is frequently utilized in clinical settings to enhance postoperative analgesia in patients.[14] During PCIA in patients after esophageal carcinoma surgery, administering dexmedetomidine in combination with sufentanil reduced the required sufentanil dosage by 22% compared to treatment with sufentanil alone during the 48-hour postoperative period. Additionally, the combined treatment also alleviated postoperative pain during rest and coughing.[15] After undergoing a partial laryngectomy, patients who received dexmedetomidine in combination with sufentanil exhibited lower VAS scores, and the demand for sufentanil among these patients decreased by 20.6%

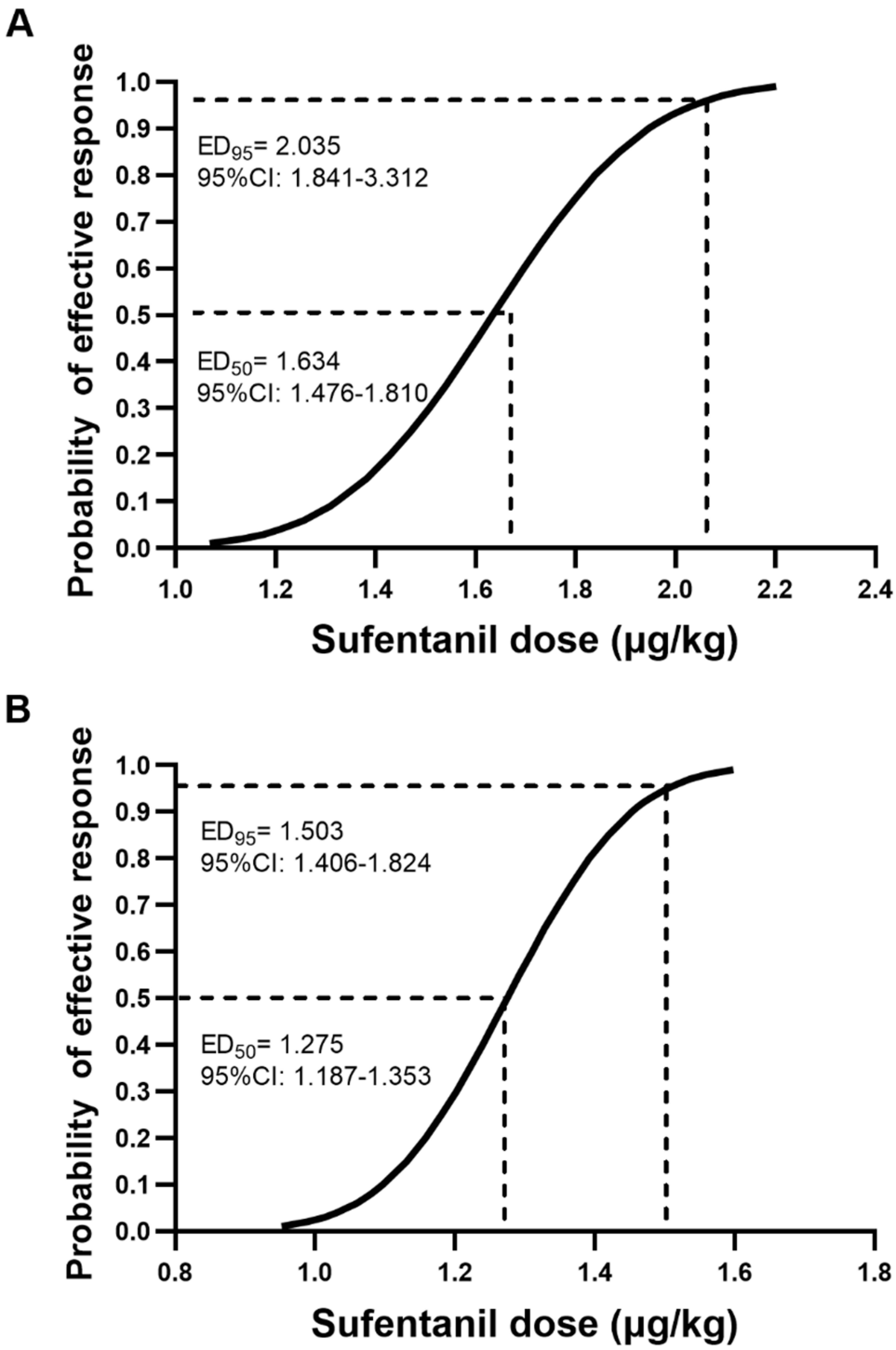

Figure 3 Dose-effect curve of sufentanil for postoperative analgesia after caesarean section in the two S group. (**A**) represents the S group, and (**B**) represents the DS group.

within 24 hours.[16] Adding dexmedetomidine to the PCA regimen of sufentanil decreased the dose of sufentanil by 18.4% within 24 hours after cesarean section, reduced the need for rescue analgesia, and improved the satisfaction of parturients.[6] In our study, we found that a significant reduction in the dose of sufentanil in the DS group (mean ± SD: 119.5 ± 17.3) compared to the S group (mean ± SD: 128.6 ± 18.5). Specifically, the doses of sufentanil and tramadol in the DS group were decreased by 7.1% and 25.8%, respectively. Patients in the DS group had lower VAS scores with rest

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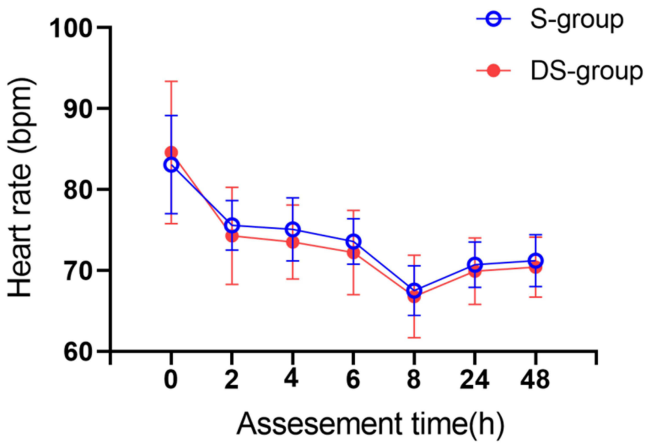

Figure 4 Changes in the heart rate at different time points in the S and DS groups.

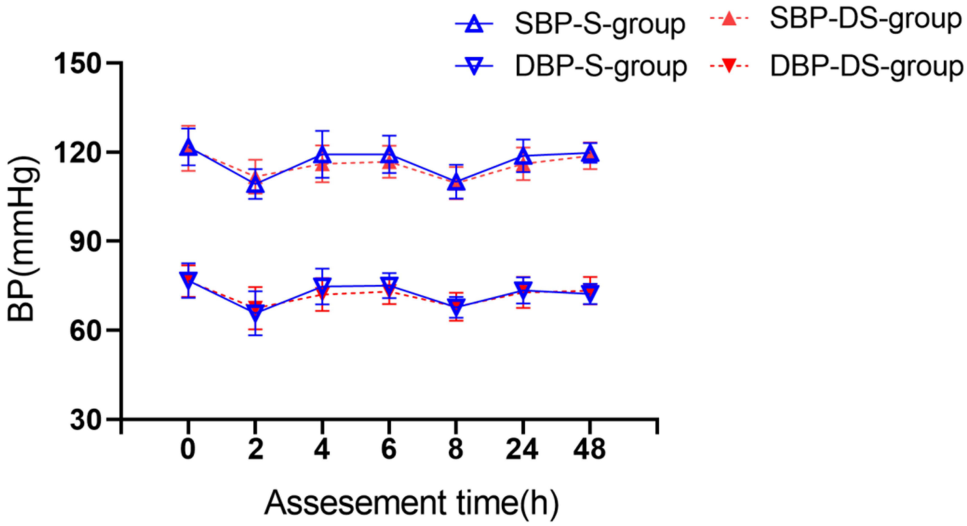

Figure 5 Changes in the blood pressure at different time points in the S and DS groups.

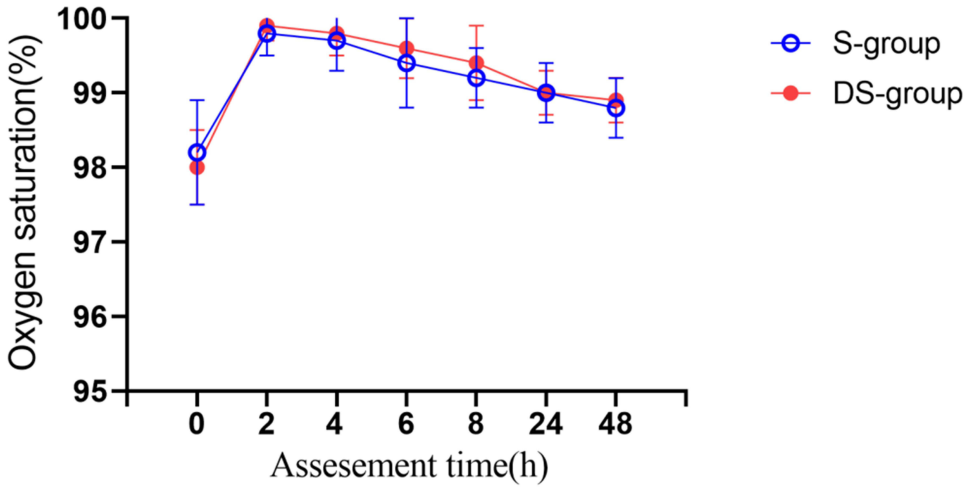

Figure 6 Changes in the pulse oxygen saturation at different time points in the S and DS groups.

Table 2 The VAS Scores During Rest and Movement at Different Time Points in the S and DS Groups

	VAS Scores During Rest, M (IOR)		P values	VAS Scores During Movement, M (IOR)		P values
Group	S(n=35)	DS(n=35)		S(n=35)	DS(n=35)	
t_2	3 (2)	3 (1)	0.080	4 (1)	4 (1)	0.980
t_3	3 (1)	2 (1)	0.088	4 (1)	4 (1)	0.212
t_4	2 (1) *	2 (1) *	0.491	4 (1)	3 (0) *#	0.003
t_5	2 (1) *	2 (1) *#	0.012	3 (0)	3 (1) *#	0.001
t_6	1 (1) *	1 (1) *	0.628	2 (1) *	2 (1) *	0.832
X^2 values	69.468	77.861		68.618	73.692	
P values	<0.001	<0.001		<0.001	<0.001	

Notes: Values are M(IQR). *p< 0.05 vs t_2; #p< 0.05 vs S group.
Abbreviations: M, Median; IOR, Interquartile Range.

Table 3 Ramsay Scores at Different Time Points in the S and DS Groups

Group	n	t_2	t_3	t_4	t_5	t_6	χ^2 values	P values
S	35	3 (1)	2 (1)	2 (1)	2 (1)	2 (1)	68.618	<0.001
DS	35	3 (1) #	3 (1) #	3 (1) #	3 (1) #	2 (1)	22.821	<0.001
P value		0.042	0.037	0.011	0.010	0.636	–	–

Notes: Values are M(IQR). #p< 0.05 vs S group.

Table 4 The Sufentanil and Tramadol Doses, PCA Times, and the First Lactation Time in the S and DS Groups

	S Group (n = 35)	DS Group (n = 35)	F values	P values
Sufentanil (ug)	128.6 ±18.5	119.5 ±17.3#	4.378	0.040
Tramadol (mg)	165.7 ±53.9	123.0 ±42.6#	13.612	<0.001
PCA (times)	6.0 ±2.6	4.7 ±2.2#	5.116	0.027
First lactation time (h)	56.9 ±3.1	51.2 ±3.7#	47.982	<0.001

Notes: Values are mean ± SD. #p< 0.05 vs S group.
Abbreviations: SD, standard deviation; PCA, Patient-controlled analgesia.

Table 5 The Adverse Reactions and Satisfaction with Postoperative Analgesia in the S and DS Groups

Adverse Reactions	S Group (n = 35)	DS Group (n = 35)	χ^2 values	P values
Hypotension, n (%)	3 (8.57)	4 (11.4)	0.159	0.690
Bradycardia, n (%)	1 (2.86)	3 (8.57)	1.061	0.614
Dizziness, n (%)	3 (8.57)	4 (11.4)	0.159	0.690
Nausea and vomiting, n (%)	11 (31.4)	4 (11.4) #	4.158	0.041
Skin pruritus, n (%)	10 (28.6)	3 (8.57) #	4.629	0.031
Satisfaction, n (%)	12 (34.3)	21 (60.0) #	4.644	0.027

Notes: Values are number of patients. #p< 0.05 vs S group.

and during movement than those in the S group. The DS group also had a lower frequency of PCA episodes. These results indicated that dexmedetomidine enhanced the analgesic effect of sufentanil and decreased the sufentanil dose required and the demand for rescue analgesia. Our results were similar to the findings reported in the above studies. This

may be due to the synergistic analgesic effects of dexmedetomidine and sufentanil.[17,18] The study revealed that patients administered dexmedetomidine in combination with sufentanil for PCA exhibited lower levels of IL-6 and TNF-α compared to those treated with sufentanil alone. This suggests that dexmedetomidine effectively mitigates the post-operative inflammatory response, which in turn leads to reduced postoperative pain sensitization.[15]

Patients who underwent thoracotomy had higher Ramsay scores when they used dexmedetomidine combined with sufentanil for PCIA than those who only used sufentanil for PCIA.[19] In our study, the Ramsay scores in the DS group were higher than those in the S group at 4 hours, 6 hours, 8 hours, and 24 hours after the operation. Our results were similar to those reported in the above study. Dexmedetomidine produces a sedative and hypnotic effect by stimulating the α-2 adrenergic receptor in the locus coeruleus, which maintains the patient in stages 2–3 of the non-rapid eye movement sleep phase. The patients remain in a sedated state, from which they can be easily woken up, and the medication does not produce respiratory inhibition, similar to natural sleep.[20,21] In our study, the Ramsay scores were less than 4 in both groups, which indicated that dexmedetomidine can provide suitable postoperative sedation but does not produce deep sedation. This may be because the dose of dexmedetomidine (0.025 μg/kg/h)used in this study was considerably lower than the recommended sedative dose of dexmedetomidine (0.2–0.7 μg/kg/h).

Early postoperative breastfeeding is essential for mothers and infants, as it can maintain the steady development of the intestinal microbiota in infants, reduce the incidence of infantile diarrhea and deaths caused by it, and decrease the long-term risk of infant diabetes and obesity.[22] It can also reduce the risk of ovarian cancer, breast cancer, postpartum depression, hypertension, cardiovascular disease, and type 2 diabetes in mothers.[23] Some studies have shown that administering dexmedetomidine during the perinatal period after cesarean section can optimize analgesia, shorten the time to first lactation, increase the lactation volume, and improve the recovery quality and comfort of parturients.[24] In this study, we found that the DS group lactated earlier than the S group, suggesting that dexmedetomidine combined with sufentanil PCIA after cesarean section can shorten the time to first lactation. This finding aligns with previous research, reinforcing the potential benefits of this combined analgesic approach in fostering early breastfeeding practices. Milk secretion is mainly regulated by prolactin and oxytocin. However, postoperative pain, anxiety, and depression can increase the release of dopamine and dynorphin, which can inhibit the secretion and release of prolactin and oxytocin, thus decreasing the secretion of breast milk.[24]

Therefore, we speculated that the shortened time to the first lactation in the DS group might be because of two reasons. First, dexmedetomidine is a highly selective α-2 receptor agonist, which can reduce the excitability of the sympathetic nervous system and the release of catecholamines; these changes can weaken the inhibitory effect of dopamine on prolactin release. Second, the DS group had lower pain scores, which might have positively influenced maternal mood and promoted the release of prolactin and oxytocin.

The primary side effects of dexmedetomidine include transient hypertension, hypotension, and bradycardia, which are caused by vasoconstriction, its effect on antisympathetic nerves, and pressure-receptor-mediated parasympathetic activation. Its hemodynamic effects on the body depend on the dosage and the rate of administration.[25] In this study, SBP, DBP, HR, and SpO_2 were similar in the two groups at each time point. Furthermore, there were no significant variations observed in the incidence of hypotension, bradycardia, or dizziness among the two groups. The parturients in the DS group were more satisfied with postoperative analgesia, and they experienced lower postoperative nausea, vomiting, and skin itching than the parturients in the S group. These results showed that the combination of dexmedetomidine and sufentanil administered through PCIA after cesarean section is safe for parturients and can effectively reduce adverse reactions, such as nausea, vomiting, and skin pruritus. One study found that the combined use of dexmedetomidine and sufentanil for analgesia after cesarean section did not increase adverse effects such as bradycardia and drowsiness, but instead reduced the occurrence of nausea, compared to the use of sufentanil alone.[24] Our findings are consistent with the results of this study. This was because the dosage of dexmedetomidine used in this study was relatively small, and the infusion speed of the analgesia pump was slow. The combined administration of dexmedetomidine reduced the dose of sufentanil, which in turn mitigated the side effects associated with opioids.

This study had some limitations. First, we only observed the effect of 1.5 μg/kg of dexmedetomidine on the analgesic effect of sufentanil. When dexmedetomidine and ropivacaine were used for labour analgesia, the EC_{50} of ropivacaine was significantly lower at dexmedetomidine concentrations of 0.4 μg/mL, 0.5 μg/mL, and 0.6 μg/mL compared to

dexmedetomidine concentrations of 0 μg/mL and 0.3 μg/mL. However, the difference in EC_{50} of ropivacaine at dexmedetomidine concentrations of 0.4 μg/mL, 0.5 μg/mL, and 0.6 μg/mL was not statistically significant.[26] This suggests that dexmedetomidine has a dose-dependent reduction of ropivacaine EC_{50} and that this dose-dependence has a capping effect. In the future, we will further explore whether dexmedetomidine has a dose-dependent reduction of sufentanil ED_{50}. Second, we only focused on the time of the first lactation but did not assess the lactation volume. Third, We did not measure the concentrations of sufentanil and dexmedetomidine in breast milk at various periods; therefore, information regarding the excretion of intravenous analgesics into maternal milk during PCIA is not available. However, a study found that after administering dexmedetomidine in parturients undergoing elective cesarean section, the concentration of dexmedetomidine in milk was significantly lower than that in plasma, and the dose was very low relative to infants, which had negligible effects on infants. Dexmedetomidine has low oral bioavailability and a very low likelihood of absorption through breast milk.[27] In our study, we closely monitored the newborn's vital signs and various physiological functions, and we also assessed lactation. No abnormalities were found.

Conclusions

In conclusion, this study found that dexmedetomidine reduced ED_{50} and ED_{95} of sufentanil in PCIA after cesarean section, reduced the need for rescue analgesia, and lowered postoperative pain scores. Additionally, dexmedetomidine provided suitable postoperative sedation, shortened the time to the first lactation, and enhanced parturients' satisfaction with the postoperative analgesia treatment.

Data Sharing Statement

For reasonable data requests, contact the corresponding author by email.

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Author Contributions

All authors made significant contributions to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; they took part in drafting, revising, or critically reviewing the article; they gave final approval of the version to be published; they have agreed that the article has been submitted to Drug Design, Development and Therapy; and they agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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