

Interaction of Analgesic Effects of Dezocine and Sufentanil for Relief of Postoperative Pain: A Pilot Study

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Purpose: The combination of dezocine and sufentanil is often used for postoperative analgesia in China and other areas, but the interaction of both two drugs is still unclear. The purpose of this study was to evaluate the interaction of the analgesic effects of dezocine and sufentanil in the patients after gynecological laparoscopic surgery.

Patients and Methods: We conducted a prospective, randomized, double-blinded clinical trial. A total of 150 patients were divided into 5 groups (30 in each group) in the post-anesthesia care unit, namely, dezocine group (Group D), sufentanil group (Group S) and dezocine mixed sufentanil groups (Group DS1-3). In group D and S, the initial dose of dezocine or sufentanil was 5mg and 5μg intravenously, respectively. In Group DS1, the initial dose was dezocine 5mg × 3/4 and sufentanil 5μg × 1/4. In Group DS2, the initial dose was dezocine 5mg × 1/2 and sufentanil 5μg × 1/2. In Group DS3, the initial dose was dezocine 5mg × 1/4 and sufentanil 5μg × 3/4.

Results: The median effective dose (ED₅₀) of dezocine and sufentanil alone was 3.92 (95% confidence interval (CI) 3.01~4.64) mg and 3.71 (95% CI 2.78~4.39) μg, respectively. The isobolographic analysis showed that the combination of dezocine and sufentanil at 1:3, 1:1 or 3:1 appeared in the additive line.

Conclusion: In conclusion, when simultaneously administered intravenously, combined dezocine and sufentanil produce an additive effect for relieving the acute nociception after gynecological laparoscopic surgery.

Keywords: dezocine, sufentanil, analgesia, intravenous, laparoscopy

Introduction

Dezocine, a mixture of partial μ-receptor agonist and κ opioid receptor antagonist, is widely used to manage postoperative pain in China and other areas, because it reduces adverse reactions compared with pure μ receptor agonists.¹⁻⁴ Sufentanil acts selectively as the μ-receptor agonist to produce strong analgesic effect. The potent opioid may induce many adverse events including respiratory depression, nausea, vomiting and other adverse reactions in a dose-dependent manner after surgery.⁵

Either in pharmacological experiments or clinical practice, the combined application of different drugs could change the strength or properties of the original drug, such as the joint application of analgesics to relieve pain and reduce corresponding adverse reactions.⁶⁻⁹ Between two drugs, the pharmacodynamic interactions are called synergistic, additive, or antagonistic meaning that the magnitude of the effects is large, equal, or small compared to the effects of the original drugs, respectively.^{10,11}

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Dezocine combined with μ -receptor agonists, such as sufentanil, is a commonly used method in postoperative analgesia in clinic.¹² However, the interaction between dezocine and sufentanil is unclear. Therefore, the purpose of this study was to evaluate the analgesic effects of dezocine and sufentanil administered to patients following gynecological laparoscopic surgery.

Materials and Methods

Ethics Approval, Registration and Patient Selection

This was a prospective, randomized, double-blinded study conducted from June to December 2019 in one single center. This study had been approved by the Ethics Committee of the Tianjin Central Hospital of Gynecology Obstetrics (2019KY033) and was registered at the Chinese Clinical Trial Registration Center (ChiCTR 1,900,021,270) before patients' enrollment. Written informed consent was obtained from all participants before surgery. This trial was conducted in accordance with the Declaration of Helsinki. The study was reported according to the CONSORT checklist.

Before gynecological laparoscopic surgery, patients were instructed on self-evaluation of pain using the numerical rating scale (NRS) (0 represented no pain and 10 represented the worst pain the patient has experienced). Patients (18 to 60 years old and body mass index (BMI) $18\text{--}30\text{kg.m}^{-2}$) were enrolled in the study if presented with $\text{NRS} > 4$ and American Society of Anesthesiologists Physical (ASA) physical status I or II. Patients were excluded if they had dezocine or sufentanil allergy, a history of chronic use of other opioids or analgesics, antipsychotic drugs, other comorbid conditions, cognitive impairment and conversion to open surgery.

After entering into the post-anesthesia care unit (PACU), the patients were divided into 5 groups ($n=30$), namely, dezocine group (Group D), sufentanil group (Group S) and dezocine mixed sufentanil groups (Group DS1, 2 and 3). Randomization was achieved using computer-generated random codes which were concealed in opaque envelopes. All participants as well as observer and statistical analyst were blinded to the grouping allocation except for the nurse who prepared the medication.

Study Procedures

Patients did not receive any premedication and were monitored by noninvasive arterial pressure, electrocardiography, peripheral pulse oxygen saturation and bispectral index (BIS) at the operating room. Each patient was induced with sufentanil

$0.5\mu\text{g.kg}^{-1}$, propofol 2 to 2.5mg.kg^{-1} and cisatracurium 0.2mg.kg^{-1} . According to hemodynamic parameters, remifentanyl $0.20\text{--}0.25\mu\text{g.kg.min}^{-1}$ and propofol $6\text{--}10\text{mg.kg.h}^{-1}$ were infused intravenously to maintain anesthesia. During the operation, P_{ETCO_2} and BIS values were maintained at $35\text{--}45\text{mmHg}$ ($1\text{mmHg}=0.133\text{kPa}$) and $40\text{--}50$, respectively. After the trachea was extubated, patients were transported to the PACU.

Pain intensity was assessed using NRS in PACU. During the 1 h stay in PACU, vital signs were monitored continuously. If NRS was 4 or greater, the patient was enrolled in the study. The doses were tested by a sequential method. In Group D, an initial dose of 5mg dezocine (dezocine injection, 5mg.mL^{-1} , Yangzi Jiang Pharmaceutical Group Co., Ltd. China) was administered intravenously. An initial dose of $5\mu\text{g}$ sufentanil (sufentanil injection, $50\mu\text{g/mL}$, Yichang Ren Fu Pharmaceutical Co., Ltd. China) was administered intravenously in Group S. Based on isobolographic investigation of the interaction between the two drugs,^{13,14} three different ratios were prepared as dezocine: sufentanil = 3:1, 1:1 and 1:3. In Group DS1, the initial dose was dezocine $5\text{mg} \times 3/4$ plus sufentanil $5\mu\text{g} \times 1/4$ (ratio of dezocine: sufentanil = 3:1). In Group DS2, the initial dose was dezocine $5\text{mg} \times 1/2$ and sufentanil $5\mu\text{g} \times 1/2$ (ratio of dezocine: sufentanil = 1:1). In Group DS3, the initial dose was dezocine $5\text{mg} \times 1/4$ and sufentanil $5\mu\text{g} \times 3/4$ (ratio of dezocine: sufentanil = 1:3). In all groups, the dose-adjusted gradient was one-fifth of the initial dose, and the drugs were added into normal saline to a total of 5 mL. The dose of dezocine or sufentanil administered to each patient was determined by the response of the previous one in that group and adjusted to a higher or lower dose. The up-down sequential allocation technique was described by Dixon and Massey.^{15,16}

The analgesic efficacy was defined as the $\text{NRS} \leq 3$ or a decrease in NRS by more than 50% within 15 minutes (min) after administration. Drugs were administered by a clinic nurse, who was trained on how to prepare the medication. At 15 min, patients with ineffective analgesia were given rescue analgesia and administered oxycodone and ketorolac tromethamine titration if necessary.

Outcome Measurements

Vital parameters were collected routinely. Patients were monitored for adverse events including nausea, vomiting, pruritus, and dizziness. Drowsiness was assessed using the Ramsay sedation score (1 = the patient was anxious and agitated; 2 = the patient was awake, tranquil, and cooperative; 3 = the patient was drowsy but responded briskly to whispering; 4 = the

patient was in light sleep and could be woken up by loud calls; 5 = the patient was asleep and responded sluggishly to loud calls; and 6 = the patient was in a deep sleep and unresponsive to calls). A Ramsay sedation score >4 was defined as excessive sedation.

Statistical Analysis

The median effective dose (ED₅₀) was defined as a median dose leading to half of patients having NRS ≤ 3 or NRS decreased by more than 50% within 15 minutes after administration using the up-and-down method.¹⁷ The analysis was performed with SPSS 18.0 (SPSS, Inc., Chicago, IL). Demographic data were presented as mean (SD). After assessing the normality of the data, one-way ANOVA was used to determine the difference. Non-normally distributed data were assessed by Kruskal–Wallis test. A *P*-value of <0.05 was considered significant.

The analgesic effect of dezocine and sufentanil was evaluated by isobolographic analysis. In the isobologram, the ED₅₀ of the two drugs used alone is plotted on the X and

Y axes, and the two points are connected to form an additive line. At the same time, 95% CI of ED₅₀ are plotted on X and Y axes, and corresponding upper and lower bounds are two lines, respectively. The area between the two lines is 95% CI of the additive line. If the ED₅₀ of drug combination application falls in the region, it means that the two drugs are addition; if it falls on the left side of the region, it represents synergy; if it falls on the right side of the region, it is antagonistic.^{18,19}

Up-down estimates were also derived from the terminal six runs of patients using the up-down method using the formula of Dixon,¹⁷ and the number of cases was about 25. We chose 30 cases to increase statistical power, and the values obtained were closer to the true values of the theory.

Results

Patient Characteristics

A total of 306 patients having gynecological laparoscopic surgery were assessed for eligibility; 150 were enrolled and randomized, and 156 were excluded according to the criteria (Figure 1). The five groups were comparable in

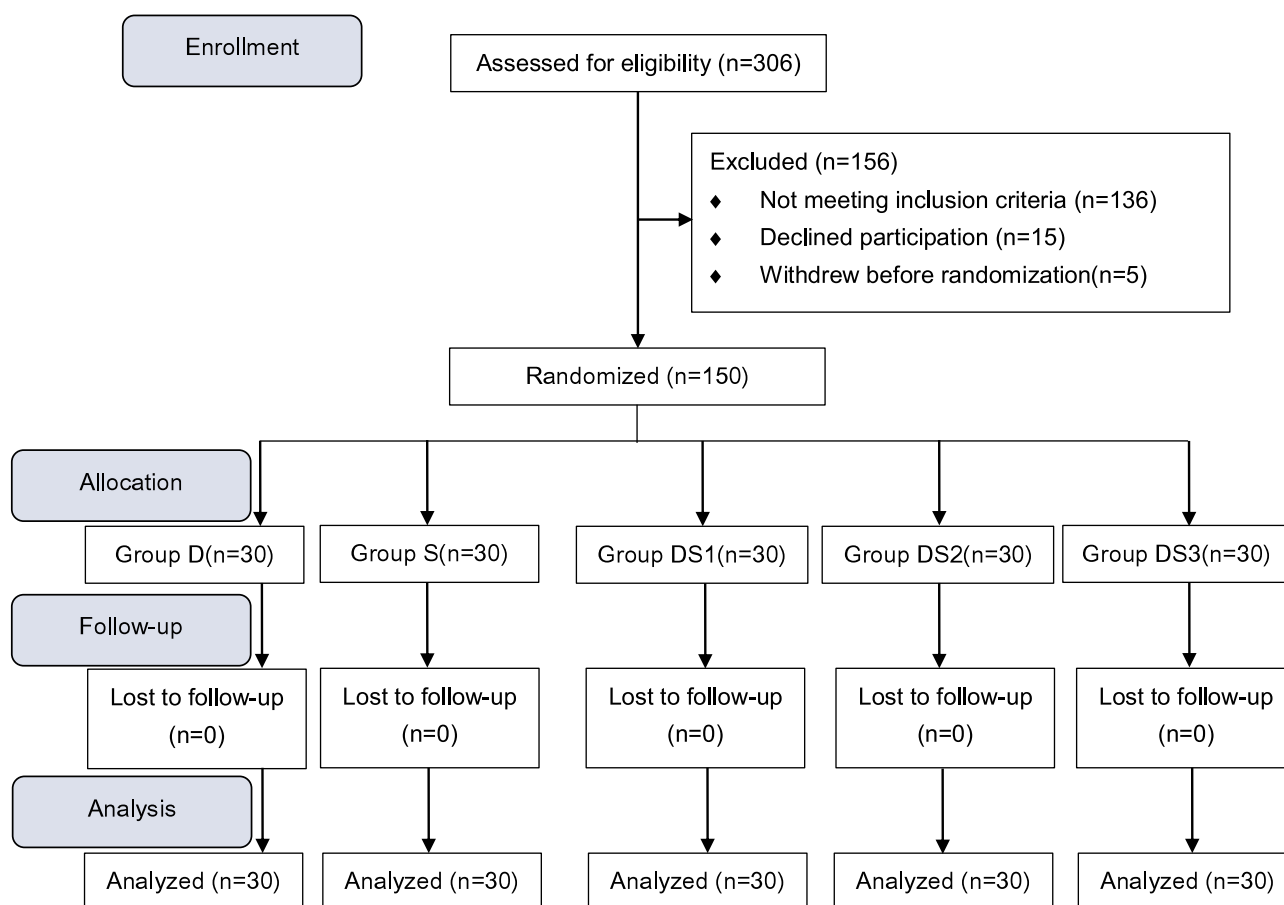


Figure 1 CONSORT diagram of patients recruitment.

Table 1 Demographic Data and Surgery-Related Information

Parameter	Group D (n = 30)	Group S (n = 30)	Group DS1 (n = 30)	Group DS2 (n = 30)	Group DS3 (n = 30)	P-value
Age; y	36(10)	37(12)	36(11)	38(11)	37(11)	0.435
BMI; kg/m ²	23(2)	22(2)	22(2)	21(2)	24(2)	0.324
ASA status; I/II	20/10	19/11	22/8	20/10	21/9	0.267
Duration of surgery; min	83(23)	87(21)	80(22)	85(27)	81(26)	0.213
NRS score on PACU admission	5(1)	6(1)	5(1)	6(1)	6(1)	0.546
Type of surgery(n)						
Hysterectomy	15	13	16	15	14	0.132
Myomectomy	10	12	7	9	11	
Enucleation of ovarian cyst	5	5	6	6	5	

Note: Data are expressed as mean (SD) or number.

Abbreviations: BMI, body mass index; NRS, numerical rating scale; Group D, dezocine group; Group S, sufentanil group; Group DS1, ratio of dezocine:sufentanil = 3:1; Group DS2, ratio of dezocine:sufentanil = 1:1; Group DS3, ratio of dezocine:sufentanil = 1:3.

terms of age, BMI, ASA status, duration of surgery, NRS score on PACU admission and surgical types. There were no significant differences with respect to baseline characteristics ($P > 0.05$) (Table 1).

Outcomes

Using the Dixon methodology, the estimated ED₅₀ (95% CI) of five groups are shown in Table 2. Individual responses to dezocine and sufentanil using Dixon's up-and-down method are presented in Figure 2. The isobolographic analysis showed that the combination of dezocine and sufentanil in a ratio of 3:1(C), 1:1(D) or 1:3(E) appeared in the additive line, which would probably be simply additive, as shown in Figure 3. Three patients (two cases in Group D and one in Group S) experienced nausea and pruritus within one hour. Ramsay sedation score >4 or other side effects were not reported.

Discussion

In this study, we have determined the ED₅₀ of dezocine and sufentanil administered alone and in combination in the postoperative period after gynecological laparoscopic surgery. Our results demonstrated an additive interaction between dezocine and sufentanil in different ratios of 1:3,

1:1, and 3:1, respectively. No serious side effects were observed. To our knowledge, this was the first study to evaluate the interaction of dezocine and sufentanil.

Previous work identified that dezocine, a mixture of partial μ -receptor agonist and κ opioid receptor antagonist,^{20,21} was not categorized as a controlled substance and had been used for postoperative analgesia for many years. Dezocine was also discovered as an inhibitor of norepinephrine, serotonin reuptake and σ -1 receptor in vitro.²¹

The analgesic efficacy of dezocine was similar to that of morphine,^{1,2,20,22} and the combined use of dezocine with morphine greatly increased the analgesic effects, which indicated that dezocine may have an additional mechanism of analgesic effect,^{23,24} and alleviating morphine-induced dependence without addiction.²²

Previous study showed that the interaction of dezocine and morphine depended on the sequence. In that study, morphine 0.15 mg/kg produced no additional effect if given after a prior dose of dezocine. But in a reverse sequence, dezocine increased the respiratory depression of morphine and also produced a dramatic increment in analgesia, which suggested an additive action.²³ We believe that there may be several reasons for the

Table 2 ED₅₀ (95% CI) of Five Groups

	Group D (n = 30)	Group S (n = 30)	Group DS1 (n = 30)	Group DS2 (n = 30)	Group DS3 (n = 30)
Dezocine; mg	3.9 (3.0~4.6)		2.7 (2.0~3.2)	1.7 (1.3~2.0)	0.8 (0.4~1.1)
Sufentanil; μ g		3.7 (2.8~4.4)	0.9 (0.7~1.1)	1.7 (1.3~2.0)	2.5 (1.2~3.3)

Abbreviations: ED₅₀, median effective dose; 95% CI, 95% confidence interval; Group D, dezocine group; Group S, sufentanil group; Group DS1, ratio of dezocine:sufentanil = 3:1; Group DS2, ratio of dezocine:sufentanil = 1:1; Group DS3, ratio of dezocine:sufentanil = 1:3.

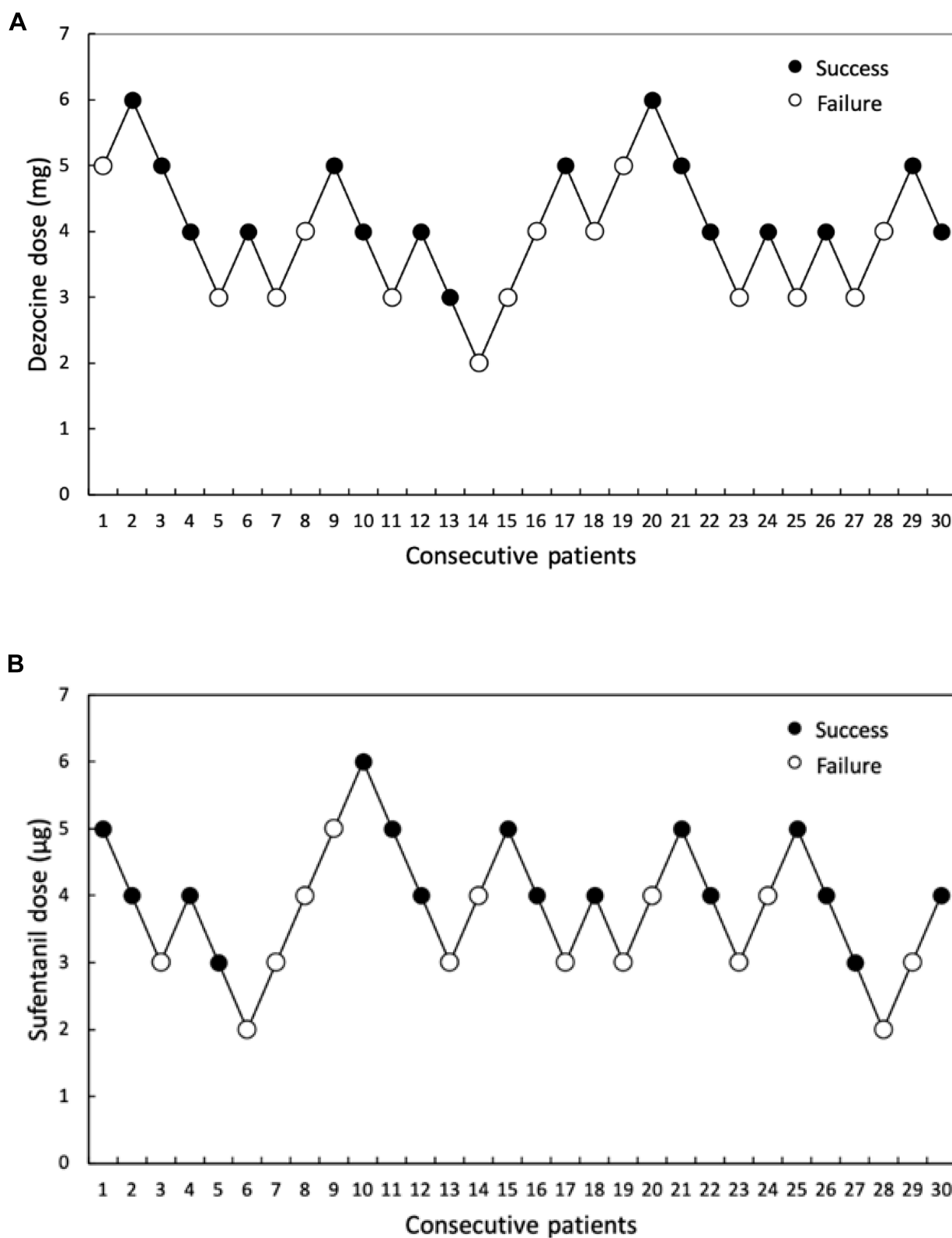


Figure 2 Sequence of dosing in the two groups of consecutive patients and their corresponding dose of the two drugs: dezocine (**A**), sufentanil (**B**). The quality of analgesia was measured on a numerical rating scale (NRS) (from 0 to 10) and was defined as effective ($\text{NRS} \leq 3$ or decreased by more than 50% within 15 minutes after administration), otherwise it would be ineffective.

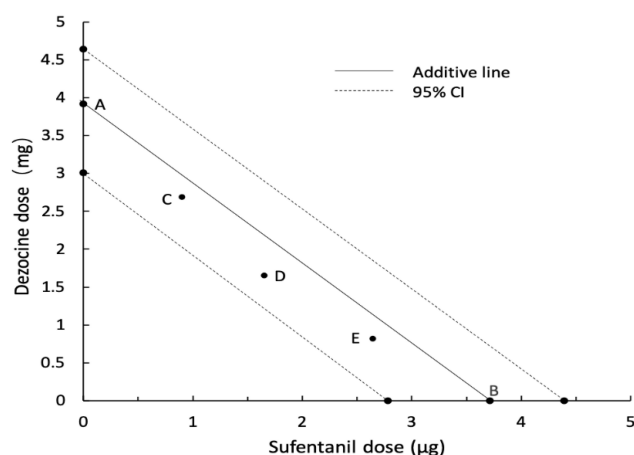


Figure 3 Isobologram (illustration) for ED₅₀ of the maximum in which the dose of dezocine alone is A = 3.9mg and sufentanil alone is B = 3.7µg. Points C (dezocine 2.7mg, sufentanil 0.9µg), D (dezocine 1.7mg, sufentanil 1.7µg) and E (dezocine 0.8mg, sufentanil 2.5µg) represent the ED₅₀ of group DS1, DS2 and DS3, respectively.

Abbreviations: ED₅₀, median effective dose; 95% CI, 95% confidence interval; Group DS1, ratio of dezocine:sufentanil = 3:1; Group DS2, ratio of dezocine:sufentanil = 1:1; Group DS3, ratio of dezocine:sufentanil = 1:3.

inconsistency between this study and the report of Gal et al. Firstly, the subjects selected by Gal did not receive μ receptor agonists before the use of dezocine and morphine, but in this study, dezocine and sufentanil were administered simultaneously, and all subjects had received μ receptor agonists before administration, which was different from the background of Gal's test. Secondly, subjects received 0.15 mg/kg dezocine and morphine in that study, which was much higher than the highest dose selected in this study. And last, the analgesic mechanism of morphine derives mainly from binding to the μ opioid receptor and less to the κ opioid receptor. Sufentanil is recognized as a selective μ receptor agonist.

A theoretical additive dose of the combination in the same component ratio was computed from the equieffective dose of the single drugs. The isobolograms were constructed following previous studies.^{10,25} In our study, the results demonstrated that additive interactions were produced by combinations of dezocine with sufentanil. Points C, D and E were located in the area between the two additive lines, which indicated that partial μ -receptor agonist/antagonist dezocine combined with sufentanil at different proportions could provide additive analgesic effects and decrease anesthetic doses. Similar to our results, it has been reported that dezocine could decrease analgesic requirement when jointly applied with other opioids.^{3,12}

Meanwhile, the additive effect of dezocine and opioid might prevent dynorphin from binding to spinal κ receptor in the central pathway of nociceptive transmission.^{20,26} In addition, dezocine could inhibit serotonin and norepinephrine reuptake providing analgesic effects, which had been implicated in the descending pain pathways.^{27–29}

The present study has several advantages. First, this study included a common range of drug ratio in clinical practice, not only including 1:1, but also 1:3 and 3:1, so the results obtained are more reliable. Second, isobolographic analysis may provide much more insight into the interactions among drugs because both drugs were combined in a dose-dependent manner (at various proportions of the fixed-ratio combinations).^{6,30–32} It can be used directly, accurately, qualitatively and quantitatively to guide clinical drug use.

This study has several limitations. Firstly, participants in our study were divided according to an equivalent dose (dezocine:sufentanil = 1000:1). If using calculated ED₅₀ of the drugs, there may be discrepancies between the two methods. Secondly, patients were recruited from laparoscopic operations. It is difficult to extrapolate the findings of the study to the patients with open surgeries. The interaction between dezocine and sufentanil needs to be investigated for other populations or more advanced surgery. Thirdly, although the ED₅₀ is not as clinically relevant as the ED₉₅, it is a simple rigorous pharmacologic approach, which could help define the pharmacodynamic interactions between two drugs. Furthermore, intraoperative approach to pain management (remifentanyl infusion) could have influenced the postoperative pain management and dezocine-sufentanil interaction/effectiveness. Further studies should assess the related adverse reactions of the combination of the two drugs and their place in the management of acute postoperative pain when different intraoperative pain management plan is used, including opioid sparing techniques (eg, multimodal pain management approach, combined spinal general anesthesia and/or quadratus lumborum block).^{33–35}

In conclusion, when simultaneously administered intravenously, combined dezocine and sufentanil produce an additive effect for relieving the acute nociception after gynecological laparoscopic surgery. Dezocine could to some extent enhance the analgesic effects of sufentanil and/or to reduce the requirement for sufentanil for acute pain management in the postoperative period.

Data Sharing Statement

Individual deidentified participant data is not going to be shared. All available data have been shown in the article and no other study-related document will be made available.

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Disclosure

The authors report no conflicts of interest in this work.

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