



# Nalbuphine 20 mg combined with sufentanil 2 µg/kg exerts a better postoperative analgesia effect in patients undergoing a second cesarean section: a randomised trial

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**Background:** Pain management following cesarean section remains a challenge, with many puerpera suffering from severe acute postoperative pain. And for a second cesarean section the degree of uterine contraction pain is more severe and frequent than that of a primipara. This study investigated the effect of different doses of nalbuphine combined with sufentanil for postoperative analgesia in patients undergoing a second cesarean section.

**Methods:** We prospectively recruited 168 women with a scarred uterus undergoing elective second cesarean section and they were randomly divided into 4 groups by random number extraction. A single intravenous injection of different doses of nalbuphine was given before the intravenous drip of oxytocin, and visual analogue scale (VAS) scores of uterine contraction pain were recorded 10 minutes before intravenous infusion of oxytocin (T1) and 10 minutes (T2), 30 minutes (T3), and 60 minutes (T4) after intravenous infusion of oxytocin. At 4, 8, 12, 24, and 48 hours after patient-controlled intravenous analgesia (PCIA), pain intensity was reassessed using the VAS score.

**Results:** One hundred and sixty patients underwent elective second cesarean section in between December 2020 and May 2021 completed the study. The VAS scores of uterine contractions at T1 and T4 were 3 (1.0), while the VAS scores at T2 and T3 were 7 (1.0), 6 (1.0), 5 (1.0), 5 (1.0) and 8 (1.0), 5 (2.0), 3 (1.0), 3 (0.75). The VAS scores at 12 hours after surgery of nalbuphine 10mg and sufentanil (NS1), nalbuphine 10 mg and sufentanil 20 mg (NS2) and nalbuphine 30 mg and sufentanil 20 mg (NS3) were lower than sufentanil (S) group ( $P < 0.001$ ). Compared with the S group, total amount of sufentanil and PCIA compression numbers in the NS1, NS2, and NS3 groups at 4–8 and 8–12 hours after surgery decreased ( $P < 0.001$ ), with a more significant decrease in the NS2 and NS3 groups than in the NS1 group ( $P < 0.001$ ). The NS3 group had a significantly higher incidence of dizziness and sleepiness ( $P = 0.02$ ,  $P = 0.001$ ). Compared with the NS2 and NS3 groups, the incidence of respiratory depression in the S group was significantly higher ( $P = 0.001$ ).

**Conclusions:** A single intravenous injection of nalbuphine 20 mg 10 minutes before the infusion of

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oxytocin combined with sufentanil 2 µg/kg could be safely used for postoperative analgesia in patients undergoing a second cesarean section and could effectively inhibit uterine contractions induced by oxytocin and reduce adverse reactions.

**Trial Registration:** Clinical Trial Registry ChiCTR2100042382.

**Keywords:** Analgesic effect; nalbuphine; scarred uterus; second cesarean section; sufentanil

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## Introduction

In recent years, the proportion of cesarean sections in China has been increasing, including repeated cesarean sections (1), which affects breastfeeding (2). And it can also cause severe uterine contractions and paroxysmal pain in the lower abdomen (3). Due to scarred uterine hyperalgesia, long operation time, poor uterine elasticity, increased uterine involution and contraction, and increased oxytocin requirements in females receiving a second cesarean section, the degree of uterine contraction pain is more severe and frequent than that of a primipara (4-6).

Nalbuphine is a new synthetic opioid receptor agonist-antagonist that agonizes κ receptors and antagonizes µ receptors. Previous studies have reported that nalbuphine can effectively inhibit visceral pain and has strong analgesic and sedative effects (7,8). Uterine contraction pain induced by postpartum oxytocin is a form of visceral pain, and thus nalbuphine may have a better analgesic effect. At present, patient-controlled intravenous analgesia (PCIA) with sufentanil (a µ-receptor agonist) is usually used clinically to relieve maternal pain (9) and can effectively relieve the level of incision pain but is not effective for oxytocin-induced uterine contractions. As a result, puerpera tend to increase the dose of sufentanil by pressing the PCIA pump to relieve pain, but this may increase the incidence of postoperative nausea, vomiting, dizziness, and sleepiness (10). Nalbuphine combined with sufentanil can reduce the dosage of opioids, thus reducing the incidence of adverse reactions (11).

In this study, we investigated the post-cesarean section analgesia effect of nalbuphine combined with sufentanil in patients undergoing a second cesarean section. A single intravenous injection of nalbuphine 10 minutes before the infusion of oxytocin was performed, starting with the low dose of the safe dose of nalbuphine 1 to the end of the maximum dose (10–30 mg) (12). The postoperative analgesia effects as well as adverse reactions were evaluated,

and the optimal dose of nalbuphine was determined. Our findings may provide evidence for developing analgesia strategies for patients undergoing a second cesarean section. We present the following article in accordance with the CONSORT reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-1026/rc>).

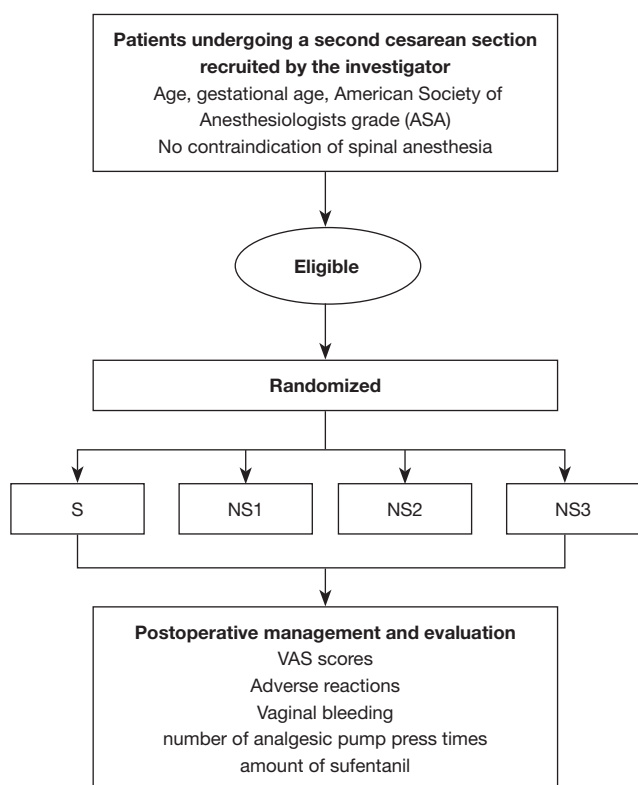
## Methods

### Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This prospective, randomized, controlled trial was approved by the Ethics Committee of The First People's Hospital of Yunnan Province (KHLL2021-KY015), and patients or their families signed an informed consent form. One hundred and sixty-eight parturients undergoing a second cesarean section between December 2020 and May 2021 were enrolled in this study, and they were randomly divided into 4 groups by random number extraction. The clinical research design was showed in *Figure 1*.

### Sample size calculation

The sample size was calculated on the basis of a pilot study that showed the effect of acupuncture on labor pain intensity and labor duration (13). The VAS score for significant pain reduction during labor was one score based on visual analogue scale (6,14). Using the PASS software 15.0,  $\alpha=0.05$ , and power =0.85, considering SD =1.4 and  $M_0=7.2$  for the labor pain score and 10% drop out of subjects, the sample size was calculated to be 36 patients for each group. To prevent excessive withdrawal, 168 patients who underwent a second cesarean section at The First People's Hospital of Yunnan Province between December 2020 and May 2021 were enrolled.



**Figure 1** Flow chart of the trial design. Note: S group, sufentanil 2 µg/kg; NS1 group, nalbuphine 10 mg + sufentanil 2 µg/kg; NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg. ASA, American Society of Anesthesiologists grade; VAS, visual analogue scale.

### Inclusion criteria

- (I) Second cesarean section;
- (II) 37 weeks ≤ gestational age <42 weeks;
- (III) Aged 20–40 years old and weight of 52–85 kg;
- (IV) American Society of Anesthesiologists (ASA) grade I–II, subarachnoid anesthesia, and without intake of opioids before surgery.

### Exclusion criteria

- (I) Patients with contraindications to intraspinal anesthesia;
- (II) History of allergy to local anesthetics and opioids, and opioid abusers;
- (III) Severe organic diseases or abnormal blood coagulation;
- (IV) Intraoperative changes in surgical procedures or methods of anesthesia, and major hemorrhage-related

factors such as placental abruption, placenta previa, and pre-eclampsia, or mental disorders.

### Randomization

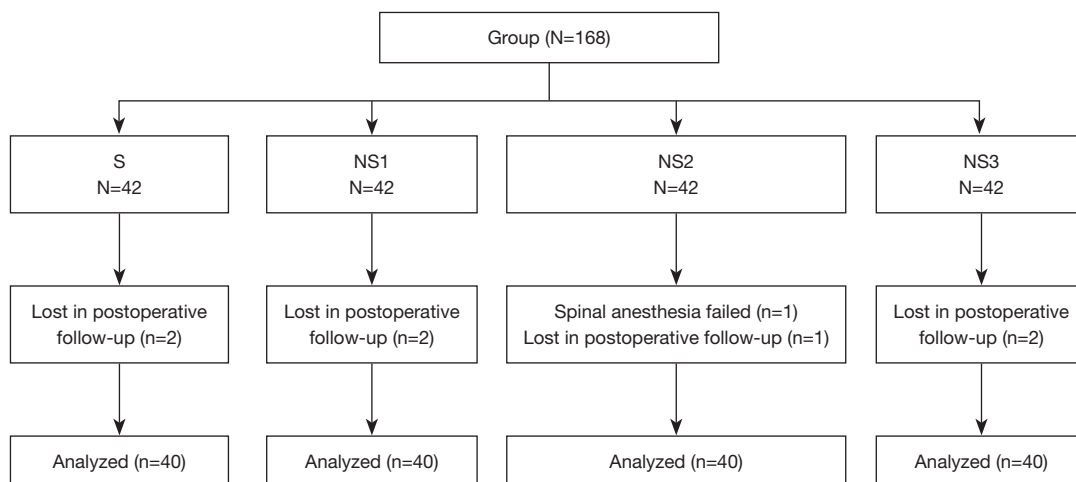
We use the SPSS software to generate random numbers in a 1:1 ratio and divided them into four groups. The group results were sealed in envelopes and kept at the beginning of the study until the end. Study members distributed the randomized results of the recruited patients. For each enrolled patient, anesthesia was administered by a dedicated anesthesiologist and intraoperative data collection was performed by researchers. Postoperative follow-up will be conducted by investigators not involved in the management of anesthesia. There was no communication between the anesthesiologist and the researcher during data collection.

### Anesthesia method

The parturients were in the left decubitus position. Spinal block anesthesia was performed at the L3-L4 spinous process space with 0.5% ropivacaine 2 mL (15 mg). During the operation, when the blood pressure decrease was greater than 30% of the preoperative base value, intravenous injection of ephedrine (0.5 mg) was performed. When the heart rate was less than 60 beats/minute, atropine (0.25–0.5 mg) was given intravenously. The anesthesia-related operations and preparation of the analgesic pump were performed by the same anesthesiologist. The cesarean section was conducted by the same obstetrician, and the postoperative evaluation was completed by another anesthesiologist in a blinded manner.

### Procedures

For all patients, PCIA was performed immediately before the first intravenous infusion of oxytocin. The parameters were set to sufentanil 0.04 µg/kg/h, flow rate 2 mL/h, 2 mL volume each compression, and locking time 15 minutes. The patients were randomly divided into 4 groups. The S group received sufentanil (2 µg/kg) by PCIA. The NS1 group received a single intravenous injection of nalbuphine (10 mg) 10 minutes before intravenous infusion of oxytocin + sufentanil (2 µg/kg) by PCIA. In the NS2 group, a single intravenous injection of nalbuphine (20 mg) 10 minutes before intravenous infusion of oxytocin + sufentanil (2 µg/kg) by PCIA was administered. Patients in the NS3 group received



**Figure 2** Flow chart of patients included in this study. Note: S group, sufentanil 2  $\mu\text{g}/\text{kg}$ ; NS1 group, nalbuphine 10 mg + sufentanil 2  $\mu\text{g}/\text{kg}$ ; NS2 group, nalbuphine 20 mg + sufentanil 2  $\mu\text{g}/\text{kg}$ ; NS3 group, nalbuphine 30 mg + sufentanil 2  $\mu\text{g}/\text{kg}$ .

a single intravenous injection of nalbuphine (30 mg) 10 minutes before intravenous infusion of oxytocin + sufentanil (2  $\mu\text{g}/\text{kg}$ ) by PCIA.

### Gathering of indicators

VAS scores of uterine contraction pain were recorded 10 minutes before intravenous infusion of oxytocin (T1) and 10 minutes (T2), 30 minutes (T3), and 60 minutes (T4) after intravenous infusion of oxytocin. At 4, 8, 12, 24, and 48 hours after PCIA, VAS scores for incision pain, number of analgesic pump press times, and amount of sufentanil were evaluated and recorded. Uterine contraction intensity was assessed with a uterine palpation score: 0–1 point, soft palpation and weak contraction; 2–3 points, moderate palpation and contraction; and 3–5 points, hard palpation and normal contraction. Vaginal bleeding was recorded, and a cumulative volume of vaginal bleeding less than 200 mL at 48 hours after operation was considered normal. Adverse reactions such as nausea, vomiting, dizziness, sleepiness, chills, pruritus, and respiratory depression were also recorded.

### Statistical analysis

Subjects who completed the study according to the study protocol were analyzed. Patients with missing values were excluded from the trial. The primary analysis will be by per-protocol (PP). All statistical analyses were performed using SPSS 26.0 software (IBM SPSS, Armonk, NY, USA). Continuous variables are expressed as mean  $\pm$  standard

deviation (SD) and compared by analysis of variance (ANOVA). For repeated measurement data, multivariate test repeated measures ANOVA or Friedman non-parametric repeated measures ANOVA was used for analysis. Nonnormal quantitative data are expressed as medians [interquartile range (IQR)] and calculated using nonparametric tests. Chi-square test was used to compare categorical variables, which are represented by n (%). All P values are two sided.

## Results

One hundred and sixty-eight patients who with a scarred uterus underwent elective second cesarean section in The First People's Hospital of Yunnan Province between December 2020 and May 2021 were included. Three patients were transferred to general anesthesia because of the poor effect of spinal anesthesia, and five patients were lost in postoperative follow-up. Finally, the data of 160 patients were analyzed, 40 in each group (Figure 2).

### Patient's baseline clinical characteristics

There was no statistically significant difference in age, height, weight, operation time, and local anesthetic dosage among the 4 groups ( $P > 0.05$ ) (Table 1).

### Pain effect evaluation

For incision pain (Table 2, Figure 3), the VAS scores of the 4 groups at 12 hours after surgery were significantly higher

**Table 1** General characteristics of all enrolled patients

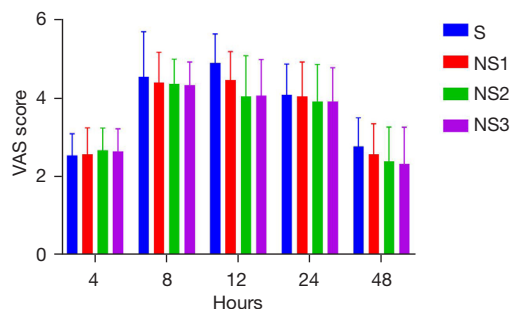
Characteristics	S group (n=40)	NS1 group (n=40)	NS2 group (n=40)	NS3 group (n=40)	P
Age, years	29.65±0.576	29.00±0.542	28.73±0.595	28.58±0.53	0.395
Height, cm	156.70±0.62	156.38±0.517	155.25±0.648	155.82±0.68	0.300
Weight, kg	66.90±1.089	67.35±1.091	65.97±0.995	66.70±1.134	0.831
Operation time, minutes	63.5 (58.0, 67.0)	61 (57.25, 66)	62 (59, 66.75)	63.5 (60.0, 67.0)	0.557
Ropivacaine dosage, mL	2 (1.9, 2.1)	2 (1.9, 2.0)	2 (1.9, 2.0)	2 (1.9, 2.0)	0.948

Note: S group, sufentanil 2 µg/kg; NS1 group, nalbuphine 10 mg + sufentanil 2 µg/kg; NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg. Age, height and weight are expressed as median ± standard deviation (M ± SD); operation time and Ropivacaine dosage are expressed as median (interquartile range) [M (IQR)].

**Table 2** VAS score of postoperative incision pain

Time	S group (n=40)	NS1 group (n=40)	NS2 group (n=40)	NS3 group (n=40)	P
4 hours	3 (1.0)	3 (1.0)	3 (1.0)	3 (1.0)	0.814
8 hours	3.25 (2.0)	4 (1.0)	4 (1.0)	4 (1.0)	0.779
12 hours	5 (1.0)	4.5 (1.0)	4 (2.0)	4 (2.0)	<0.001
24 hours	4 (1.0)	4 (1.0)	4 (2.0)	4 (1.0)	0.781
48 hours	3 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)	0.125

Note: S group, sufentanil 2 µg/kg; NS1 group, nalbuphine 10 mg + sufentanil 2 µg/kg; NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg. The VAS score of 4 groups are nonnormal quantitative data are expressed as median (interquartile range) [M (IQR)]. VAS, visual analogue scale.



**Figure 3** VAS scores for postoperative incision pain. Note: S group, sufentanil 2 µg/kg; NS1 group, nalbuphine 10 mg + sufentanil 2 µg/kg; NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg. VAS, visual analogue scale.

than those at 4 hours after surgery ( $P<0.001$ ), and the VAS scores at 24 and 48 hours after surgery were significantly lower than those at 12 hours after surgery ( $P<0.05$ ). There was no significant difference in VAS scores among the 4 groups at 4 and 8 hours after surgery ( $P>0.05$ ). VAS

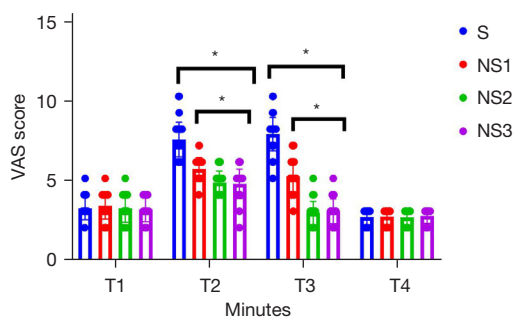
scores at 12 hours after operation in the NS1, NS2, and NS3 groups were lower than those in the S group (all  $P<0.05$ ). The VAS scores of the NS2 and NS3 groups were significantly different from those of the NS1 group ( $P<0.05$ ), while the VAS scores of the NS2 and NS3 groups were not statistically different ( $P>0.05$ ). VAS scores at 24 hours and 48 hours after surgery in the 4 groups had a downward trend, and the scores of the NS1, NS2, and NS3 groups decreased significantly ( $P<0.05$ ). For uterine contraction pain (Table 3, Figure 4), the VAS scores at T2 and T3 in the S group were significantly increased ( $P<0.05$ ) compared with those at T1, and the score at T4 was slightly lower than that at T3 ( $P<0.05$ ). In the NS1, NS2, and NS3 groups, the VAS scores at T2 and T3 increased less than that at T1 ( $P<0.05$ ), and the scores at T4 were significantly lower than those at T3 ( $P<0.05$ ), among which the VAS scores of the NS2 and NS3 groups decreased more significantly at T4 ( $P<0.01$ ). There was no significant difference in VAS scores among the 4 groups at T1 ( $P>0.05$ ). Compared with the S group, the NS1, NS2, and NS3 groups had a lower increase in VAS scores at T2, T3, and T4 (all  $P<0.001$ ). Among them,



**Table 3** VAS score of uterine contractions

Time	S group (n=40)	NS1 group (n=40)	NS2 group (n=40)	NS3 group (n=40)	P
T1	3 (1.0)	3 (1.0)	3 (1.75)	3 (1.0)	0.647
T2	7 (1.0)	6 (1.0)	5 (1.0)	5 (1.0)	<0.001
T3	8 (1.0)	5 (2.0)	3 (1.0)	3 (0.75)	<0.001
T4	3 (1.0)	3 (1.0)	3 (1.0)	3 (1.0)	0.806

Note: S group, sufentanil 2 µg/kg; NS1 group, nalbuphine 10 mg + sufentanil 2 µg/kg; NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg; T1, before intravenous infusion of oxytocin; 10 minutes (T2), 30 minutes (T3), and 60 minutes (T4) after intravenous infusion of oxytocin. The VAS score of 4 groups are nonnormal quantitative data are expressed as median (interquartile range) [M (IQR)]. VAS, visual analogue scale.



**Figure 4** VAS scores for uterine contractions. Note: S group, sufentanil 2 µg/kg; NS1 group, nalbuphine 10 mg + sufentanil 2 µg/kg; NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg. \*,  $P < 0.05$ , at time T2, there was a statistical difference between group S and the other three groups and there was a statistical difference between group NS1 and the other two groups; at time T3, there was a statistical difference between group S and the other three groups and there was a statistical difference between group NS1 and the other two groups. VAS, visual analogue scale.

the increase in scores of the NS2 and NS3 groups was more significant than that of NS1 ( $P < 0.01$ ), while there was no significant difference in VAS scores between the NS3 and NS2 groups at the 4 different time intervals ( $P > 0.05$ ). Total amount of sufentanil (Table 4) and the number of PCIA compressions (Table 5) at 8 and 12 hours after surgery were increased compared with those at 4, 24, and 48 hours after operation ( $P < 0.05$ ), of which the increase was most significant at 8 and 12 hours after operation ( $P < 0.01$ ).

### Opioid dosage assessment

There was no significant difference in the total amount

of sufentanil at 4, 24, and 48 hours after operation among the 4 groups ( $P > 0.05$ ). Compared with the S group, total sufentanil amount and the number of PCIA compressions at 12 and 24 hours after operation in the NS1, NS2, and NS3 groups were decreased (all  $P < 0.05$ ), and the reduction in the NS2 and NS3 groups was more significant than that in the S group at 12 and 24 hours after the operation ( $P < 0.01$ ). However, there was no significant difference between the NS2 and NS3 groups in the total amount of sufentanil used and the number of PCIA compressions at all 4 time intervals ( $P > 0.05$ ). The cumulative amount of vaginal bleeding in the 4 groups within 48 hours after operation was within 200 mL, and the difference was not statistically significant ( $P > 0.05$ ) (Table 6). There was no significant difference in the uterine palpation score among the 4 groups ( $P > 0.05$ ).

### Evaluation of adverse reaction rate

Compared with the S group, the NS3 group had a higher incidence of dizziness during analgesia ( $P < 0.05$ ), while the NS1 and NS2 groups had a slightly lower incidence of dizziness (Table 7). Compared with the S group, the incidence of sleepiness in the NS3 group was significantly higher during analgesia ( $P < 0.05$ ). Compared with the S group, the incidence of sleepiness in the NS1 and NS2 groups was slightly higher but significantly lower than that in the NS3 group ( $P < 0.05$ ). Compared with the NS2 and NS3 groups, the incidence of respiratory depression in the S group was significantly higher ( $P < 0.05$ ). However, the difference in the incidence of respiratory depression between NS2 and NS3 groups was not statistically significant ( $P > 0.05$ ). There were no cases of respiratory depression in the NS1 group. Compared with the NS1 and NS2 groups, the incidence of nausea was higher in the

**Table 4** Total dose of sufentanil

Group	S group (n=40)	NS1 group (n=40)	NS2 group (n=40)	NS3 group (n=40)	P
0–4 hours	14 (13, 14.75)	14 (13.0, 15.0)	14 (13.0, 14.0)	13.5 (13.0, 14.0)	0.664
4–8 hours	24 (24, 24.75)	20 (19.0, 21.0)	17.5 (17.0, 19.0)	18 (17, 18.75)	<0.001
8–12 hours	36 (35.0, 37.0)	34 (33.0, 36.0)	32 (31.0, 33.0)	32 (31.0, 34.0)	<0.001
12–24 hours	9.0 (8.0, 11.0)	9 (7.25, 11)	10 (7.25, 12)	9.5 (8.0, 11.0)	0.594
24–48 hours	2 (2.0, 3.0)	2 (2.0, 3.0)	2 (2.0, 3.0)	2 (2.0, 3.0)	0.655

Note: S group, sufentanil 2 µg/kg; NS1 group, nalbuphine 10 mg + sufentanil 2 µg/kg; NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg. The total dose of sufentanil are nonnormal quantitative data are expressed as median (interquartile range) [M (IQR)].

**Table 5** Number of analgesic pump compression times

Group	S group (n=40)	NS1 group (n=40)	NS2 group (n=40)	NS3 group (n=40)	P
0–4 hours	3 (1.0)	3 (1.0)	3 (1.0)	3 (0.75)	0.572
4–8 hours	4 (1.0)	2 (0.75)	2 (1.0)	1 (1.0)	<0.001
8–12 hours	3 (2.0)	2 (2.0)	2 (1.75)	2 (2.0)	<0.001
12–24 hours	2 (2.0)	2 (2.0)	2 (2.0)	2 (2.0)	0.969
24–48 hours	4 (1.0)	4 (2.0)	4 (2.0)	4 (2.0)	0.553

Note: S group, sufentanil 2 µg/kg; NS1 group, nalbuphine 10 mg + sufentanil 2 µg/kg; NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg. The number of analgesic pump compression times are nonnormal quantitative data are expressed as median (interquartile range) [M (IQR)].

**Table 6** Uterine contraction intensity

Indicator	Group	4 hours	8 hours	12 hours	24 hours	48 hours
Vaginal bleeding (mL)	S group (n=40)	64.83±2.49	33.58±2.13	26.68±2.83	18.38±1.76	9.83±1.19
	NS1 group (n=40)	64.95±3.00	33.90±2.61	26.13±3.28	17.80±1.62	9.98±1.13
	NS2 group (n=40)	63.90±2.31	33.45±2.52	26.60±3.09	17.88±1.59	9.70±1.28
	NS3 group (n=40)	64.80±3.18	33.93±2.39	27.50±2.95	17.35±1.56	10.30±1.34
	P value	0.494	0.812	0.396	0.125	0.297
Uterine palpation score	S group (n=40)	3.80±0.68	4.08±0.69	3.83±0.70	4.14±0.64	4.10±0.68
	NS1 group (n=40)	4.03±0.68	3.93±0.60	4.08±0.60	4.10±0.63	4.03±0.73
	NS2 group (n=40)	4.03±0.59	4.10±0.63	4.05±0.57	4.08±0.74	4.05±0.57
	NS3 group (n=40)	4.00±0.80	4.20±0.64	4.00±0.70	4.25±0.71	4.10±0.68
	P value	0.466	0.486	0.768	0.968	0.968

NS2 group, nalbuphine 20 mg + sufentanil 2 µg/kg; NS3 group, nalbuphine 30 mg + sufentanil 2 µg/kg. The Vaginal bleeding (mL) and Uterine palpation score are continuous variables are expressed as mean ± standard deviation (SD).

**Table 7** Incidence of adverse reactions

Group	Dizziness	Sleepiness	Nausea	Vomiting	Pruritus	Chills	Respiratory depression
S group (n=40)	2 (5%)	0 (0%)	2 (5%)	1 (2.5%)	0 (0%)	0 (0%)	10 (25%)
NS1 group (n=40)	1 (2.5%)	3 (7.5%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
NS2 group (n=40)	1 (2.5%)	2 (12.5%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)
NS3 group (n=40)	5 (12.5%)	10 (25%)	3 (7.5%)	1 (2.5%)	0 (0%)	0 (0%)	3 (7.5%)
$\chi^2$ value	5.063	16.699	1.643	3.019	0	0	16.699
P value	0.0203	0.001	0.837	1.0	0	0	0.001

Note: S group, sufentanil 2  $\mu\text{g}/\text{kg}$ ; NS1 group, nalbuphine 10 mg + sufentanil 2  $\mu\text{g}/\text{kg}$ ; NS2 group, nalbuphine 20 mg + sufentanil 2  $\mu\text{g}/\text{kg}$ ; NS3 group, nalbuphine 30 mg + sufentanil 2  $\mu\text{g}/\text{kg}$ . Incidence of adverse reactions are categorical variables, which are represented by n (%).

S and NS3 groups ( $P < 0.05$ ). In addition, the incidence of vomiting in the NS3 group and the S group was similar at about 2.5%, while the NS1 and NS2 groups had no vomiting cases.

## Discussion

Pain after cesarean section mainly includes incision pain and contraction pain. Incision pain, with its specific location, is a form of somatic pain. Uterine contraction pain is a form of visceral pain, which is characterized by inaccurate positioning, and mainly manifested as paroxysmal colic, mostly caused by postpartum uterine involution and paroxysmal contractions. Compared with a first cesarean section, patients receiving a second cesarean section have more severe, long-lasting, and frequent contractions and hyperalgesia (4-6).

At present, PCIA is usually used clinically for postoperative analgesia of cesarean section. Sufentanil is the most commonly used drug and can produce good postoperative analgesia, but there are many adverse reactions, including nausea and vomiting, and the inhibitory effect of uterine contractions is poor, affecting the postoperative recovery of patients (15,16). In this study, sufentanil was used for PCIA for postoperative analgesia in patients undergoing a second cesarean section. The results showed that when oxytocin was not infused (T1), the VAS scores of uterine contractions in the 4 groups of patients were within 4 points, consistent with a previous report (10). However, patients who only used sufentanil for PCIA (S group) had a significant increase in the VAS score for uterine contractions after intravenous infusion of oxytocin, with the VAS score of some parturients as high as 8 points. Meanwhile, the dosage of sufentanil and the number of

PCIA compressions increased, and respiratory depression occurred in 25% of the parturients. The results showed that only using sufentanil for postoperative analgesia in patients undergoing a second cesarean section could effectively inhibit incision pain but was not effective for oxytocin-induced uterine contractions. Also, the incidence of postoperative respiratory depression was high.

At present, there are fewer analgesic procedures for postoperative oxytocin-induced uterine contractions for patients undergoing a second cesarean section. Nalbuphine is an opioid receptor agonist-antagonist. Its action time is about 3–4 hours, and its elimination half-life is 1.9 hours. It can selectively agonize  $\kappa$  receptors to produce sedation and analgesia (17). Its analgesic effect is equivalent to that of morphine, which is effective for visceral pain (18). Nalbuphine has a limited antagonistic effect on  $\mu$  receptors and mainly antagonizes  $\mu_2$  receptors, while its effect on  $\mu_1$  receptors is weak (19). As a result, nalbuphine can reduce the incidence of nausea, vomiting, urinary retention, respiratory depression, and other adverse reactions caused by sufentanil activation of  $\mu_2$  receptors and has no obvious antagonistic effect on the analgesic effect of activated  $\mu_1$  (16,20,21). Previous studies (22,23) have shown that sufentanil combined with nalbuphine for cesarean section patients could effectively inhibit incision pain and uterine contractions and reduce the incidence of nausea, vomiting, and respiratory depression (16). However, during the analgesia period, it was found that due to the continuous intravenous pumping of nalbuphine, the mother was often in a state of sedation, and the incidence of dizziness and sleepiness increased (24). The safety of nalbuphine combined with sufentanil for post-cesarean section analgesia remains to be further evaluated. Preliminary studies (25,26) have found that sufentanil combined with nalbuphine



for PCIA after cesarean section could relieve oxytocin-induced uterine contractions, but the VAS score for uterine contractions remained high after oxytocin intravenous infusion, which may have resulted from continuous pumping of nalbuphine and the low blood concentration, leading to a poor effect on oxytocin-induced contractions. Therefore, for patients undergoing a second cesarean section in this study, we used a single intravenous injection of nalbuphine 10 minutes before intravenous infusion of oxytocin to allow nalbuphine to reach a certain blood concentration, thereby effectively inhibiting oxytocin-induced contractions.

In this study, we found that after intravenous infusion of oxytocin, compared with the S group, the VAS scores for uterine contractions at T2, T3, and T4 in the NS1, NS2, and NS3 groups were significantly reduced, and the VAS scores in the NS2 and NS3 groups decreased more significantly than the NS1 group. Our results showed that a single intravenous administration of nalbuphine 10 minutes before intravenous infusion of oxytocin had a good analgesic effect on oxytocin-induced uterine contractions (visceral pain), and the analgesic effect of intravenous nalbuphine injection of 20 or 30 mg on uterine contractions at T2, T3, and T4 was better than that of intravenous nalbuphine of 10 mg. There was no statistically significant difference in uterine contractions among the 4 groups of patients at different time intervals, and there was no significant effect on the intensity of contractions. In the NS2 group, 12.5% and 2.5% of patients had sleepiness and dizziness, respectively, and in the NS3 group, 25% and 12.5% of patients had sleepiness and dizziness, respectively. This may have been because nalbuphine stimulates  $\kappa$  receptors to produce a sedative effect, leading to a significantly higher incidence of sleepiness and dizziness in the NS3 group than in the NS2 group.

Jacqz-Aigrain *et al.* reported that the relative dose of nalbuphine ingested by infants through mother's breast milk was  $0.59\% \pm 0.27\%$  of the mother's daily dose (27), and thus after taking nalbuphine for postpartum pain, mothers can still breastfeed (27). In this study, the doses of intravenous nalbuphine in the NS1, NS2, and NS3 groups were 10, 20, and 30 mg, respectively, which was much lower than the 0.2 mg/kg/4 h used by Jacqz-Aigrain *et al.* (27) (cumulative dose was 25.5–34.5 mg/kg/d), and there was no neonatal respiratory depression. Therefore, based on the pharmacokinetics of nalbuphine (10) and the study by Jacqz-Aigrain *et al.* (27), the dose of intravenous nalbuphine selected in this study could be safely used for postoperative analgesia in patients undergoing a second cesarean section.

The main limitation of this study was that the blood concentration of nalbuphine in maternal blood, breast milk, and neonatal blood was not measured. Further studies are warranted.

## Conclusions

In summary, for patients undergoing a second cesarean section, a single intravenous injection of nalbuphine (20 mg) at 10 minutes before the infusion of oxytocin combined with sufentanil (2  $\mu\text{g}/\text{kg}$ ) could be safely used for postoperative analgesia and effectively inhibit the uterine contraction pain induced by oxytocin, producing good postoperative analgesia and reducing the occurrence of adverse reactions.

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## Footnote

*Reporting Checklist:* The authors have completed the CONSORT reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-1026/rc>

*Trial Protocol:* Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-1026/tp>

*Data Sharing Statement:* Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-1026/dss>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-1026/coif>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First People's Hospital of Yunnan Province (KHLL2021-KY015). All patients or their families have signed written informed consent.

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