

# Nalmefene relieves epidural morphine-caused pruritus following caesarean section: a randomized and placebo-controlled clinical trial

Chaochao Zhong (✉ [zhong249767626@163.com](mailto:zhong249767626@163.com))

Affiliated Hospital of Nantong University

Xingguo Xu

Affiliated Hospital of Nantong University

Xiang Zhu

Affiliated Hospital of Nantong University

Yibin Qin

Affiliated Hospital of Nantong University

Haihang Miao

Affiliated Hospital of Nantong University

Xinchong Huang

Affiliated Hospital of Nantong University

Su Cao

Affiliated Hospital of Nantong University

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## Research article

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# Abstract

**Background.** Epidural morphine has an effective analgesic effect in cesarean section patients; however, a very common adverse effect caused by epidural morphine is pruritus, which is difficult to treat or prevent. Here, we aimed to investigate whether a  $\mu$ -opioid antagonist with central and peripheral effects reduces morphine-induced pruritus.

**Methods.** In this prospective randomized trial, eighty patients scheduled for an elective cesarean section under spinal anesthesia with 3 mg of epidural morphine were assigned into the nalmefene group (n=40) or placebo group (n=40). After delivery, either 50  $\mu$ g of intravenous nalmefene hydrochloride (Nalmefene group) or an equivalent amount of normal saline (Placebo group) was administered to the patients. In the meantime, an assessment of a series of side effects such as pruritus, nausea, and pain was conducted at 2, 4, 8, 12, and 24h after epidural morphine administration.

**Results.** All eighty participants completed this trial. The total incidence of pruritus in the first 24 hours following the section was reduced in IV nalmefene group compared with the placebo group (37.5% vs 65%,  $P=0.003$ ). Moreover, IV nalmefene administration relieved the pruritus intensity, whereas the difference in the incidence of nausea and vomiting between the two groups was not significant. Besides, the nalmefene group displayed significantly higher pain scores at 8, 12 and 24h than the placebo group (all  $P<0.05$ ). However, no significant difference in the percentage of patients with an analgesic treatment was found between the two groups ( $P=0.37$ ).

**Conclusion.** In this study, a single dose of 50  $\mu$ g of IV nalmefene was found to decrease the overall severity and incidence of epidural morphine-induced pruritus, but cause no adverse effect on postoperative analgesia.

## Background

Pruritus is one of the commonest adverse effects resulting from use of epidural morphine for postoperative analgesia following cesarean section; it reportedly occurs in 30-100% of the patients<sup>1</sup>. Although pruritus does not impose a remarkable influence on the patient's health<sup>2</sup>, it causes a disagreeable sensation that elicits a scratching reflex. At present, epidural morphine is still being used in the clinic due to its excellent postoperative analgesia after caesarean delivery.<sup>1</sup>

In fact, many medications have been studied for preventing epidural opioid-associated pruritus, and morphine-induced pruritus showed no or weak response to antihistamines, serotonin antagonists, and propofol<sup>3,4</sup>. More investigations have been done on several other drugs with different effects as well as side effects, including gabapentin, nalbuphine and pentazocine. Currently, the precise mechanism underlying neuraxial opioid-caused pruritus remains unknown. As opioid receptors are highly expressed in the central nervous system<sup>5</sup>, it is generally believed that  $\mu$  receptors mediate the above pruritus. Therefore, naloxone, a  $\mu$ -opioid antagonist, can be the most effective therapeutic drug for epidural

morphine-caused pruritus. However, the use of  $\mu$ -opioid antagonists may potentially cause an adverse impact on analgesia<sup>3</sup>.

Experimental evidence suggests that naloxone alleviates the itching of animals caused by opioids<sup>6</sup>; however, it can antagonize the analgesic effect while relieving itching. Nalmefene is a derivative of naloxone, which displays higher affinity with  $\mu$  receptor as well as a long-lasting effect. Studies have shown that low doses of nalmefene have no effect on analgesia or postoperative pain<sup>7</sup>. To date, there are few studies focused on the treatment of pruritus with nalmefene. Here, we hypothesized that IV nalmefene may effectively relieve epidural morphine-caused pruritus following caesarean section.

## Methods

This study was registered on April 2, 2019, and was assigned a Chinese Clinical Trial Registry number: ChiCTR1900022268

(<http://www.chictr.org.cn/edit.aspx>). This work has been

reported in accordance with the guidelines of the Consolidated Standards of Reporting Trials (CONSORT).

In this study, a randomized and placebo-controlled trial was performed on a total of 80 patients undergoing elective cesarean section from April of 2019 to June of 2019.

We recruited the following individuals in the study: ASA class I or II women aged 18 years or older who were scheduled for an elective caesarean section under epidural anaesthesia. The following exclusion criteria were applied in this trial: no consent obtained for this study, coagulation diseases, liver or kidney failure, pre-existing itching, a history of lumbar spine surgery.

To perform epidural anesthesia, an 18-gauge epidural needle was used and an epidural catheter was inserted at the T12-L1 or L1-L2 level of the patients. 60 mg (12 ml) of 0.5% ropivacaine and 3 mg of morphine were then administered respectively. The patients were maintained at supine position, and maintenance of a systolic blood pressure of at least 100 mmHg throughout the operation was performed by using colloid liquid as well as intermittent injection of phenylephrine.

All patients were randomly assigned into the placebo group (injection with saline) and nalmefene group (injection with 50  $\mu$ g of nalmefene). Nalmefene or placebo was administered just prior to the end of surgery, and intraoperative anaesthesia and postoperative care were routinely conducted. Baseline data of the patients, including age, characteristics, and operation time, were collected. The rate of pain or nausea/vomiting during the operation was recorded. Following the operation, the severity of itching, pain scores, and other side effects such as nausea and vomiting were evaluated 2, 4, 8, 12, and 24 h after administration of nalmefene or saline, respectively. At 24 hours following delivery, patients were reexamined to determine the total incidence of pruritus, regardless of the requirement for a treatment of pruritus or pain. The assessment of pruritus intensity was performed based on verbal rating scale (0 no

pruritus, 1 mild pruritus, 2 moderate pruritus, 3 severe pruritus).<sup>3</sup> VAS scores for pain ranged from 0 (no symptom) to 10 (unbearable pain). 4 mg of Intravenous ondansetron was administered for relieving nausea and vomiting. Non-steroidal anti-inflammatory drugs or intravenous morphine were used to assist postoperative analgesia when necessary.

## Statistics

The software SPSS 13.0 was used for statistical analysis in this study. The sample size was calculated by using Power Analysis and Sample Size (PASS) software (NCSS) (LLC, UT, USA) with  $\alpha=0.05$  and  $\beta=0.95$ . Clinically, a reduction in the incidence of pruritus by 30% indicates a therapeutic significance. The preliminary analysis revealed a high incidence of pruritus (65%) in the control group. Thus, each of the groups in this study must contain no less than 32 patients in order to fulfill the requirement for a 30% reduction in the incidence of pruritus.

Levene method was used for testing normality. The normally distributed data was presented as the mean and standard deviation (SD), while the other data was presented as the mean and interquartile range. Count data groups were analyzed using chi-square test. Comparative analysis of proportional data was carried out based on the  $\chi^2$  test as well as Fisher's exact test. Nemenyi test was performed for determining the difference between the two groups. Statistically,  $P \leq 0.05$  represented a significant difference.

## Results

80 out of 84 initially enrolled patients participated in this study; all these patients were assigned into the placebo group (n=40) or the nalmefene group (n=40). As indicated in Table 1, these two groups displayed no difference in the baseline characteristics.

As summarized in Table 4, based on the primary outcome measures, the incidence of pruritus in the nalmefene group and the placebo group was 32.5% (13/40) and 65% (26/40), respectively. The difference in the incidence between the two groups was significant ( $P < 0.05$ ). Notably, while 4 patients in the nalmefene group received treatment of pruritus with ondansetron or antihistamine, 19 patients in the placebo group needed to be treated for pruritus (Table 4,  $P < 0.01$ ). Moreover, the two groups exhibited significant differences in the severity of pruritus 2, 4, 8, and 12 h after the administration of epidural morphine, respectively (Table 2,  $P < 0.05$ ).

As shown in Table 3, the two groups had similar VAS scores at 2, 4, and 24 h after the administration, whereas significantly higher VAS scores at 8 and 12 h were present in the nalmefene group compared with the placebo group. Clearly, there was no significant difference between the two groups in the number of patients receiving treatment for pain (Table 4, 10% vs 15%,  $p=0.37$ ).

The status of nausea and vomiting within the first 24 h following the operation was analyzed in all patients in Table 4. The incidence of nsusea in the placebo and nalmefene groups was 17.5% and 25%,

respectively, while the incidence of vomiting was 7.5% vs 10% between the two groups. Statistically, no significant differences in the above two symptoms were found between the two groups (nsusea, P=0.29; vomiting, P=0.51).

Fig. 1 The screening , exclusion and randomization for all patients in this study were illustrated in the chart.

Table 1. Comparative analysis of the characteristics, obstetric, and baseline clinical data of the patients between the two groups

	Placebo(n=40)	Nalmefene (n=40)
Age (y)	27.5±3.7	26.4±3.6
Weight (kg)	73.6±4.1	73.4±4.6
BMI (kg/m <sup>2</sup> )	29.9±2.7	29.9±2.8
Nulliparous	25(62.5%)	23(57.5%)
Op time (min)	46.6±4.6	45.5±4.2

Table 2. The assessment of the clinical manifestation of pruritus at 2, 4, 8, 12, and 24h following epidural injection of morphine in all patients of the two groups

	2h*	4h*	8h*	12h*	24h
Placebo group(n=40)					
No pruritus		23(57.5%)	21(52.5%)	14(35%)	34(85%) 39(97.5%)
Mild pruritus		12(30%)	12(30%)	14(35%)	6(15%) 1(2.5%)
Moderate pruritus		5(12.5%)	7(17.5%)	10(25%)	0 0
Severe pruritus		0	0	2(5%)	0 0
Nalmefene group(n=40)					
No pruritus		36(90%)	32(80%)	27(67.5%)	40(100%) 40(100%)
Mild pruritus		4(10%)	8(20%)	11(27.5%)	0 0
Moderate pruritus		0	0	2(5%)	0 0
Severe pruritus		0	0	0	0 0

Table 3. Comparative analysis of the pain VAS scores between the two groups

	2h	4h	8h*	12h*	24h	
Placebo group		1.2±0.8	1.9±0.8	2.1±0.9	2.2±0.7	2.0±0.8
Nalmefene group		1.2±0.7	1.9±1.1	2.8±0.8	3.1±0.7	2.9±0.8

Table 4. Comparative analysis of the adverse events in the two groups

	Placebo(n=40)	Nalmefene (n=40)	P
Nausea(n)	7	10	0.29
Vomitting(n)	3	4	0.51
Pruritus(n)	26	13	<0.05
treatment of pruritus(n)	19	4	<0.01
treatment of pain(n)	4	6	0.37

## Discussion

In this prospective, randomized, and placebo-controlled clinical trial, a comparative analysis was performed on the effects of nalmefene and normal saline on pruritus relief in post-caesarean section patients. Here, we showed that a single dose of 50 µg of IV nalmefene reduced the overall severity and incidence of epidural morphine-induced pruritus, but caused no adverse effect on the postoperative analgesia.

Pregnant women are more prone to itching that occurs in the face, neck, and upper thorax; the incidence of itching among these women is dose dependent<sup>8,9,10</sup>. While the precise mechanisms of pruritus is still not clear, a lot of progress has recently been made in identifying signal molecules as potential targets for anti-pruritus therapies<sup>11,12</sup>. As µ-opioid receptor antagonists can effectively relieve pruritus by acting on central and probably peripheral targets<sup>13</sup>, the interactions of opioid with µ-opioid receptors may mediate opioid-induced pruritus. With the increased knowledge, we can identify more therapeutic targets and then improve the efficacy of the pruritus treatments as well as reducing the adverse effects. As an µ receptor antagonist, naloxone has been shown to be the most effective therapeutic drug for pruritus caused by epidural morphine. However, only a small dosage of naloxone can be applied for relieving pruritus following caesarean delivery, due to the fact that a high dosage of naloxone antagonizes the analgesic action of opioids<sup>14</sup>. As a novel µ-opioid antagonist derived from naloxone, nalmefene has a stronger affinity with µ-opioid compared with naloxone. While both naloxone and nalmefene can easily cross the blood-brain barrier<sup>15</sup>, naloxone is metabolized faster in the body. Importantly, the clinically used dose of nalmefene appears to antagonize the side effects of opioids, but cause little effect on the pain.

In this clinical trial, we analyzed the effect of nalmefene on epidural morphine-caused pruritus, and found that nalmefene administration decreased the incidence of pruritus to 32.5%. Compared with the previous reports<sup>16,17</sup>, a higher percentage of pruritus was observed in this study. The above discrepancy may be attributed to the varied dosage of morphine used in the studies. Besides, the higher rate of pruritus observed in this trial may result from the improper dosage and administration time, or the fact that nalmefene does not affect other itching transmitters, such as prostaglandins<sup>18</sup>, the neurotransmitters glutamate and GABA<sup>19</sup>, and NMDA receptors<sup>20</sup>.

In the present study, we observed that while the two groups had similar VAS scores at 2, 4, and 24 h after epidural injection of morphine, slightly higher VAS scores at 8 and 12 h were evident in the nalmefene group compared with the placebo group. This observation suggested that nalmefene reduced pruritus and impaired the analgesic efficacy of epidural morphine. Surprisingly, no discrepancy in the percentage of patients receiving analgesic treatment was detected between the two groups, suggesting that nalmefene reduces the overall severity and incidence of epidural morphine-caused pruritus, but has no adverse effect on postoperative analgesia. In addition to itching, epidural morphine causes nausea as well as vomiting due to the activation of serotonin receptors in the trigger area of the vomiting chemoreceptor<sup>21</sup>. In the study, we showed that the difference in both nausea and vomiting was not significant between the two groups.

There are some limitations in this clinical trial. First, we only analyzed the effect of a single dose of nalmefene on relieving epidural morphine-caused pruritus in patients following Caesarean section. Therefore, a change in the dosage of nalmefene or the type of patients may yield different results. Secondly, testing a dose-dependent effect of nalmefene on pruritus is still lacking in the study. Thus, future studies will determine whether the anti-pruritus effect of nalmefene is dose-dependent. If it was the case, we need to further identify the optimal dose of nalmefene that can be applied for relieving pruritus as well as reducing the side effects on analgesia to the greatest extent. Moreover, it would be important to investigate whether nalmefene also displays a therapeutic effect on pruritus caused by other opioids with epidural administration.

## Conclusions

This study revealed that a single dose of 50 µg of IV nalmefene decreases the overall severity and incidence of epidural morphine-caused pruritus, but causes no adverse effect on postoperative analgesia.

## Abbreviations

ASA: American society of anesthesiology; VAS: visual analog scale

PASS: Power Analysis and Sample Size

## Declarations

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hospital Affiliated with Nantong University (approved number: 2018-K067). The written informed consent was obtained from each of the participants.

## Consent for publication

We acknowledge that upon the publication, the ownership of copyright for this work will be transferred to the journal "BMC anesthesiology". We declare that this work was original research, and all authors participated in drafting, revising, and approving the submitted manuscript.

## Availability of data and materials

We presented all necessary supporting data in the paper. Upon request, the datasets used in this study can be available from the corresponding author.

## Competing interests

The authors declare that no competing interests exist in the paper.

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## Authors' contributions

CCZ performed the clinical trials, and wrote the manuscript. XGX and XZ and HHM conducted the statistical analysis as well as working in the data collection. YBQ and SC worked in revising the manuscript. Each of the authors read the manuscript and approved the final version.

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## Statement

The study adheres to CONSORT guidelines.

## Authors' Information

Chaochao Zhong, Email: [zhong249767626@163.com](mailto:zhong249767626@163.com)

Xingguo Xu, Email: [TDFYXXG@126.com](mailto:TDFYXXG@126.com)

Xiang Zhu, Email: [Bobofly8850@sina.com](mailto:Bobofly8850@sina.com)

YiBin Qin, Email: [572537172@qq.com](mailto:572537172@qq.com)

Haihang Miao, Email: [miaohaihang@163.com](mailto:miaohaihang@163.com)

Xinchong Huang, Email: [hxcnt115@sohu.com](mailto:hxcnt115@sohu.com)

Su Cao, Email: [mzkcs@sina.com](mailto:mzkcs@sina.com)

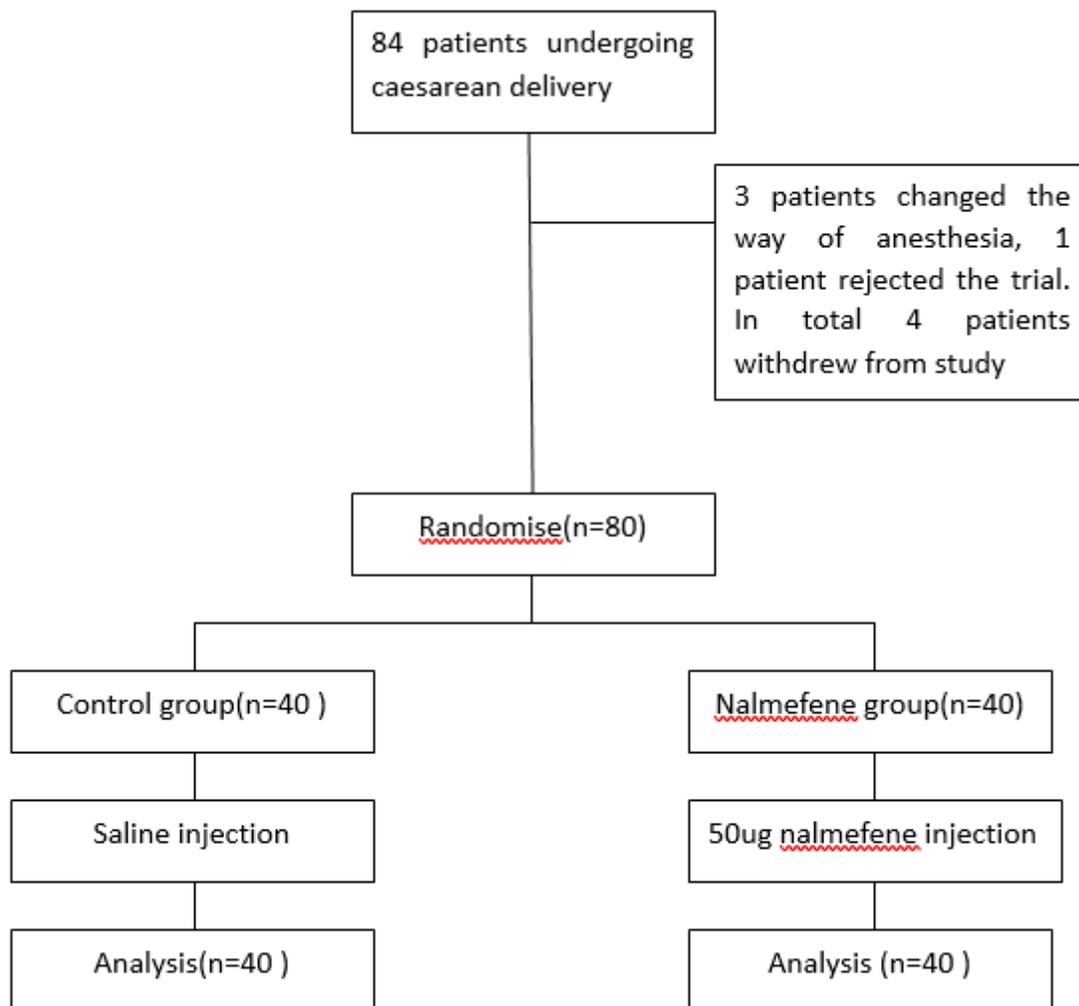
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## Figures



**Figure 1**

patient enrollment flow diagram. This illustrates the flow of all patients screened, excluded, and randomized

## Supplementary Files

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