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Nalbuphine versus dexmedetomidine for treatment of combined spinal-epidural post-anesthetic shivering in pregnant women undergoing cesarean section

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Abstract

Objective: This study aimed to compare the clinical efficacy and side effects of nalbuphine and dexmedetomidine for treatment of combined spinal-epidural anesthetic shivering in women after cesarean section.

Methods: A total of 120 pregnant women, who underwent elective cesarean section under combined spinal-epidural anesthesia, were enrolled in a double-blind, randomized study. These women were randomized into three groups of 40 pregnant women each to receive either saline (group C), nalbuphine 0.07 mg/kg (group N), or dexmedetomidine 0.5 μg/kg (group D) for treatment of shivering after anesthesia. The main outcome measure was a significant reduction in the time required for shivering after intervention.

Results: The mean time to cessation of shivering in groups N and D was significantly shorter than that in group C (3.5±2.7 and 4.2±3.7 versus 14.5±1.4 minutes). The success rate of shivering treatment and Observer's Assessment of Alertness/Sedation scores in groups N and D were significantly higher than those in group C, while the recurrence rate was lower than that in group C.

Conclusion: Nalbuphine 0.07 mg/kg can be used safely and effectively for shivering in pregnant women under combined spinal-epidural anesthesia.

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Nalbuphine, dexmedetomidine, combined spinal-epidural anesthesia, shivering, caesarean section, pregnant woman

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Introduction

Spinal anesthesia is the most common type of anesthesia in cesarean section surgery with an incidence of 30% to 55% for intraoperative shivering.[1] Shivering, which is a thermoregulatory response to hypothermia or muscle activity with tonic or clonic patterns,[2] mainly occurs in the upper limbs, neck, and jaw muscles. Shivering also occurs in normothermic patients with the following mechanisms: inhibition of the spinal reflex, decreased sympathetic activity, pyrogen release, and adrenal gland suppression.[3] However, perioperative hypothermia is the main cause of post-anesthetic shivering due to inhibition of the thermoregulatory mechanism induced by neuraxial anaesthesia.[2] Perioperative shivering not only increases the psychological stress response, but also leads to an increase in oxygen consumption (up to 400%).[4] Additionally, increased production of carbon dioxide results in accumulation of hypoxia and lactic acid in tissue. This then affects the process of anesthesia and surgery, causing severe consequences for pregnant women with poor cardiopulmonary function reserve.[5]

At present, there are many clinical treatments available for patients to control shivering after spinal anesthesia, including nonpharmacological methods and pharmacological methods. Non-pharmacological methods using equipment to maintain a normal temperature of the body are effective, but expensive, and lack practicality.[2] However, pharmacological methods using drugs, such as dexmedetomidine, nalbuphine, tramadol, and meperidine, are easier to carry out.

Meperidine is widely used in clinical surgery for its analgesic property. However, after patients experienced severe complications by overusing meperidine as reported in several cases, people realized that a high dosage of meperidine was associated with an increased risk for normeperidine toxicity.[6,7] Therefore, new drugs for post-anesthetic shivering need to be explored. The anti-shivering effect of meperidine is mediated by its κ-receptor and α2-receptor activities.[8] Nalbuphine is a synthetic agonist antagonist opioid that has the characteristics of μ-antagonist and κ-agonist activities. Nalbuphine has a high affinity for κ-opioid receptors in the central nervous system.[3,9] As a central α2-receptor agonist, dexmedetomidine reduces anxiety and relieves pain without development of respiratory depression.[10] Bicer et al.[11] suggested that dexmedetomidine effectively decreases post-anesthetic shivering.

This double-blind, randomized, controlled study was designed to compare the efficacy (time to cessation of shivering), complications, and side effects between nalbuphine and dexmedetomidine for treatment of combined spinal-epidural anesthesia shivering in pregnant women after cesarean section.

Materials and methods

Participants and study design

This trial was registered at the Chinese Clinical Trial Registry (ChiCTR1900023431). The study was approved by the Ethics Committee of the Affiliated Shenzhen

Maternity and Child Healthcare Hospital of Southern Medical University and informed consents were obtained from all participants.

Healthy pregnant women who were scheduled for cesarean delivery under combined spinal-epidural anesthesia were eligible for this study. Inclusion criteria were as follows: participants were scheduled for elective low segment caesarean section under combined spinal-epidural anesthesia, aged 20 to 35 years, and with American Society of Anesthesiologists (ASA) class II. ASA class II was defined as mild diseases only without substantive functional limitations. Examples of ASA class II include (but are not limited to) the following: current smoker, social alcohol drinker, pregnancy, obesity (body mass index >30 and $<40\,kg/m^2$), well-controlled diabetes mellitus/hypertension, and mild lung disease.[12] Exclusion criteria were as follows: participants had contraindication of preoperative cesarean section, pregnancy complication, contraindication of spinal anesthesia, scarred uterus, fetal distress, heart disease, history of psychoactive medication, recent fever, uncertain of anesthetic effects, high mental stress, and intraoperative blood infusion.

A total of 120 pregnant women were randomly assigned in a 1:1:1 ratio. Group C was the control group and received 0.9% normal saline intravenous injection. Group N received an intravenous injection of nalbuphine 0.07 mg/kg. Group D received an intravenous injection of 0.5 μg/kg dexmedetomidine.

Anesthetic process

Before surgery, the pregnant women had preoperative routine fasting without access to water. After entering the operating room, routine electrocardiographic monitoring was performed, and a standard cotton sheet without being warmed and oxygen with a mask were offered to the women. The oxygen flow rate was 5 L/minute, and the operating room was controlled at 22°C to 24°C. Additionally, the ASTOFLOPLUS intravenous fluid warmer (No. 201600109; Stihler Electronic GmbH, Stuttgart, Germany) was used during the operation. After establishment of venous access, a rapid intravenous infusion of heated sodium chloride 500 mL was performed within 20 to 30 minutes. The pregnant women were positioned in the left lateral position, and the L3–L4 gap was selected as the puncture point. A 25-gauge needle was used to puncture into the subarachnoid space. The spinal anesthesia formula was 0.5% ropivacaine 2 mL. At the end of the surgery, 1.5 mg of morphine (180604-1) was administered through an epidural catheter for postoperative analgesia, and the anesthetic plane was adjusted to T4. We closely observed changes in vital signs and corrected hypotension (if blood pressure dropped more than 20% of the baseline value). All operations were performed by the same experienced senior attending anesthesiologist.

On the basis of the study by Wrench et al.,[13] shivering was graded using the following scale: Grade 0, no shivering; Grade 1, vertical and/or peripheral vasoconstriction and peripheral cyanosis, but no muscle fasciculation; Grade 2, only one group of muscles had muscle fibrillation; grade 3, fibrillation of more than one group of muscles; and Grade 4, whole body muscle fasciculation.

At the moment of delivery, the anesthesiologist evaluated the pregnant women's shivering grade. If the grade of shivering was 3 or 4 on the shivering scale, the anesthetic nurse who was not involved in this study went to pick up the prepared medicine box in the anesthesia preparation room. All of the drugs for participants were prepared in the medicine box by a pharmacist in the morning (nalbuphine [10 mg/mL, 2 mL], dexmedetomidine [100 μg/mL, 2 mL], and normal saline [0.9%, 10 mL]). Therefore, the anesthetic nurse could take the drugs according to the serial number. Five minutes

following delivery, if the women's shivering scale remained at grade 3 or 4, the anesthesiologist gave all of the drugs in the syringe. The administration time was recorded, and the observation was continued until the end of the operation. The time at which a considerable reduction in shivering was observed was recorded. Additionally, the time at which the surgery ended was recorded.

Observational indices

The primary endpoint was a significant reduction in shivering time (i.e., the grade of shivering was reduced from 3 or 4 to 0 or 1). Additional analysis evaluated the occurrence of side effects, including bradycardia, hypotension, and nausea, postoperative plasma glucose and insulin levels, and sedation scores. The sedation score (improved Observer's Assessment of Alertness/Sedation [OAA/S] score[14]) was determined as follows: 1 point, conscious; 2 points, lethargy and a slow response to a normal call; 3 points, no response to a normal call, but response to a loud call; 4 points, no response to a loud call, but response to a pat on the body; and 5 points, deep sedation with the eyes closed and response to an injurious stimulus.

The time from the end of anesthesia to the start of shivering, and success and recurrence of shivering treatment were recorded. Cessation of shivering after 15 minutes of drug treatment was defined as successful treatment. Treatment failure was defined as when shivering did not stop after 15 minutes of drug treatment. Recurrence of shivering before being sent out of the postanesthesia care unit was defined as shivering recurrence. If treatment of shivering failed or relapsed, an intravenous injection of pethidine 30 mg was provided to stop the shivering.

After the pregnant women entered the recovery room, vital signs were detected, and blood samples were taken to measure blood glucose and insulin levels. A postoperative intravenous indwelling needle was used again 24 hours after surgery to measure blood glucose and insulin levels. The visual analog scale (VAS) score of uterine contraction pain was also recorded.

Randomization

The pregnant women were randomly assigned by permutation. The random process was composed of computer-generated random lists that were allocated between six and eight permutations. Notably, the process was performed by statisticians who were not involved in the follow-up study. Additionally, these statisticians were responsible for creating two identical sealed envelopes of the subjects' test regimen on the same day. One envelope was given to the anesthetic nurses who dispensed the drug and was destroyed once completed. The other envelope was given to the supervisor of the experiment in case of any emergency during the experiment. Each participant was assigned a consecutively numbered vial of either nalbuphine, dexmedetomidine, or normal saline each day by an anesthesiologist based on a randomized list.

Blinded allocation of drugs

The pregnant women were randomly divided into three groups. The drugs were uniformly placed in an opaque medicine box that contained the original solution of nalbuphine (10 mg/mL, 2 mL), dexmedetomidine (100 μg/mL, 2 mL), normal saline (0.9%, 10 mL), and a 1-mL syringe. Each solution had the same appearance. Additionally, each medicine box contained a computer-generated table of random numbers, and the box was stored in the anesthetic preparation room adjacent to the operating room. Notably, one solution was administered to only one participant, and the rest were discarded. Each syringe was labeled with a number. The subjects,

researchers, and anesthesiologist or statistician in charge of the case did not know the contents of each numbered syringe. Patients and operators (anesthesiologists, observers, and tape recorders) were not aware of the grouping. An anesthetic nurse who was not involved in the study prepared a solution of the drug and a coding envelope for the pregnant woman. The researchers in charge of collecting the data did not know the study's purpose.

Statistical analysis

IBM SPSS Statistics for Windows, version 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data are shown as mean ± standard deviation or number (%). Comparisons were made using one-way analysis of variance (ANOVA). Post hoc pairwise comparison was performed using the t-test or Kruskal–Wallis test for non-normally distributed variables and the Nemenyi test for normally distributed variables. Comparisons of categorical data were made using Pearson's chi-squared test. *P* values were adjusted by the Bonferroni test for post hoc pairwise comparison and Fisher's exact test was used to compare proportions. A P value < 0.05 was considered statistically significant.

Sample size

A power analysis was conducted to determine the number of participants required in this study. The α for the ANOVA was set at 0.05. To achieve a power of 0.80, the means of the three groups were estimated as 3, 4, and 14; the common group standard deviation was estimated as 14. A total sample size of 120 was required to detect a significant model (using the one-way ANOVA statement in the POWER procedure to compute the sample sizes[15]).

Results

Participants' baseline data

A total of 200 pregnant women were enrolled in this study from June to December, 2017. We excluded 17 women who did not meet the incision criteria, 23 women who refused to participate in the study, and 40 women who did not have considerable shivering. Finally, 120 eligible participants with Wrench grade 3 or 4 were included in the final analysis, with 40 in each group (Figure 1). The numbers of pregnant women with grade 3 were 23 in group C, 21 in group N, and 22 in group D. The numbers of pregnant women with grade 4 were 17 in group C, 19 in group N, and 18 in group D. There were no significant differences in age, height, weight, ASA classification, shivering classification, operation time, and infusion quantity among the groups (Table 1).

Comparison of shivering cessation time and treatment outcome among the three groups

There was no significant difference in the time from the end of anesthesia to the start of shivering among the three groups (Table 2). The mean time to cessation of shivering after injection of the drug was significantly shorter in groups N and D than in group C ($P < 0.05$). Because the success rate of shivering treatment in groups N (0.07 mg/kg) and D (0.5 μg/kg) was higher than that in group C ($P < 0.0001$), a two-sided α for the chi-squared test was set at 0.05, with a power of 0.90. Recurrence of shivering was significantly lower in groups N and D than in in group C ($P < 0.0001$), with a two-sided α for the chi-square test set at 0.05 and the power was 0.90 (Table 2).

OAA/S sedation score

The proportion of the OAA/S sedation score (1 point) was significantly higher in

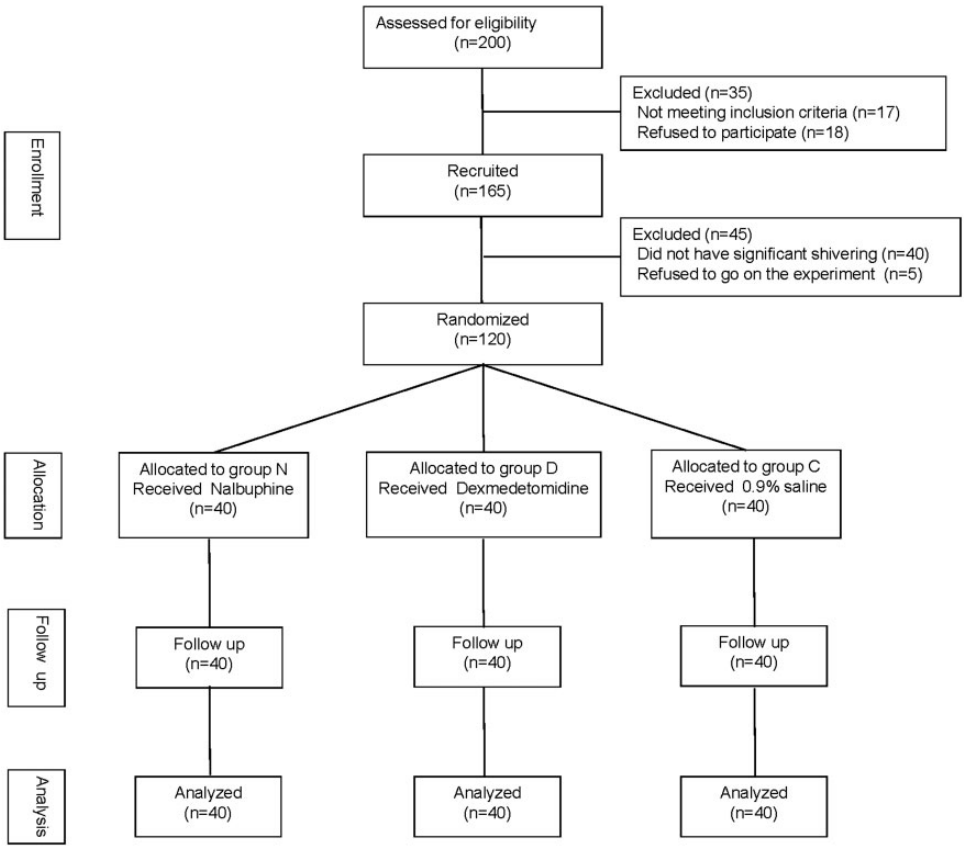

Figure 1. Flow chart of the pregnant women's recruitment.

Table 1. Demographic data in the study groups.

Variable	Group C (n = 40)	Group N (n = 40)	Group D (n = 40)	*P* value
Age (years)	30.9 ± 3.4	31.5 ± 3.9	31.8 ± 3.5	0.5653
Height (cm)	159.4 ± 4.0	159.8 ± 4.6	161.2 ± 4.6	0.1480
Weight (kg)	67.2 ± 2.7	67.9 ± 8.3	69.1 ± 5.7	0.3743
ASA (I/II)	37/3	38/2	36/4	0.368
Shivering grade (3/4)	23/17	21/19	22/18	0.973
Duration of surgery (minutes)	45.2 ± 3.5	46.0 ± 2.7	44.2 ± 3.2	0.1896
Infusion quantity (mL)	860.0 ± 62.4	840.0 ± 62.6	850.0 ± 7.6	0.3801

Data are mean ± standard deviation or number (%). Comparison of continuous data was made using one-way analysis of variance and pairwise comparison was made using the Kruskal–Wallis test for non-normally distributed variables. Comparison of categorical data was made using Pearson's chi-squared and Fisher's exact tests.
ASA: American Society of Anesthesiologists.

Table 2. Assessment of shivering and the response time and treatment outcome of shivering in the three groups.

Index	Group C (n = 40)	Group N (n = 40)	Group D (n = 40)	*P* value
Onset of shivering (minutes)	15.1 ± 2.5	15.0 ± 3.1	15.7 ± 3.0	0.4543
Successful time for shivering treatment (shivering rate reduced from 3/4 to 0/1) (minutes)	14.5 ± 1.4	3.5 ± 2.7*	4.2 ± 3.7*	<0.0001
Time interval from treatment to cessation of shivering (minutes)	14.8 ± 0.6	3.8 ± 2.6*	4.7 ± 3.5*	<0.0001
Success rate	7 (17.5)	38 (95.0)*	36 (90.0)*	<0.0001
Recurrence rate	6 (85.7)	5 (13.2)*	3 (8.3)*	<0.0001

Data are mean ± standard deviation or number (%).
*$P<0.0001$ compared with group C.
Group C: control group; group N: received an intravenous injection of nalbuphine 0.07 mg/kg; group D: received an intravenous injection of 0.5 μg/kg dexmedetomidine.

Table 3. OAA/S sedation score.

OAA/S score	Group C (n = 40)	Group N (n = 40)	Group D (n = 40)	*P* value
1 point	40 (100.0)*	20 (50.0)	5 (12.5)	<0.0001
2 points	0 (0)	14 (43.3)	13 (32.5)	<0.0001
3 points	0 (0)	6 (6.7)#	12 (30)	<0.0001
4 points	0 (0)	0 (0)#	5 (12.5)	<0.0001
5 points	0 (0)	0 (0)#	5 (12.5)	<0.0001

Data are number (%). OAA/S: Observer's Assessment of Alertness/Sedation.
*$P<0.0001$ compared with groups N and D; #$P < 0.0001$ compared with group D.
Comparisons were made using Pearson's chi-squared test. *P* values were adjusted by the Bonferroni test for post hoc pairwise comparison and Fisher's exact test was used for proportions.
Group C: control group; group N: received an intravenous injection of nalbuphine 0.07 mg/kg; group D: received an intravenous injection of 0.5 μg/kg dexmedetomidine.

group C than in groups N and D ($P < 0.0001$). The proportions of OAA/S sedation scores, including 3, 4, and 5 points, were significantly higher in group D than in group N (all $P < 0.0001$) (Table 3).

Complications in the three groups

Among the side effects, four (10%) pregnant women each in group C and group N experienced bradycardia, and 15 (37.5%) pregnant women had bradycardia in group D. Therefore, the incidence of bradycardia was significantly lower in group N than in group D ($P < 0.05$). There were no significant differences in the incidence of nausea and hypotension among the three groups (Table 4).

Comparison of the VAS score of uterine contraction pain

VAS scores of uterine contraction pain were significantly increased 24 hours after surgery compared with those in the postpartum room ($P < 0.05$) (Table 5) Significantly less women required remedial

Table 4. Complications in the three groups.

Complication	Group C (n=40)	Group N (n=40)	Group D (n=40)	*P* value
Bradycardia	4 (10)	4 (10)	15 (37.5)*	0.009
Hypotension	4 (13.3)	5 (16.7)	4 (13.3)	0.672
Nausea	3 (7.5)	5 (12.5)	6 (15.0)	0.269

Data are number (%).
P<0.05compared with groups C and N.
Group C: control group; group N: received an intravenous injection of nalbuphine 0.07 mg/kg; group D: received an intravenous injection of 0.5 μg/kg dexmedetomidine.

Table 5. Comparison of the VAS score of uterine contraction pain.

Variable	Group C (n = 40)	Group N (n = 40)	Group D (n = 40)	*P* value
VAS score in the postpartum room	0.6 ± 0.6	0.5 ± 0.6	0.6 ± 0.5	0.9948
VAS score 24 hours after surgery	5.7 ± 0.9*	3.2 ± 0.8*#	4.6 ± 0.8*	<0.0001
Remedial analgesics required 24 hours after surgery (number)	35	5*	25	0.269
Lactation start time (hours)	25.1 ± 4.6	24.7 ± 4.7	25.2 ± 5.3	0.8679

Data are mean ± standard deviation or number. VAS: visual analog scale.
The remedial analgesic drug was nalbuphine, with a dosage of 0.2 mg/kg.
*$P<0.05$ compared with the VAS score in the postpartum room within the same group; #$P<0.05$ compared with group D.
Group C: control group; group N: received an intravenous injection of nalbuphine 0.07 mg/kg; group D: received an intravenous injection of 0.5 μg/kg dexmedetomidine.

analgesics in group N than in group C ($P < 0.05$). There was no significant difference in the time starting lactation among the groups.

Comparison of plasma glucose and insulin levels among the three groups

Plasma glucose and insulin levels were significantly increased 24 hours after surgery compared with those measured in the postpartum room in all of the three groups (all $P < 0.05$). The mean plasma glucose level was significantly lower in group N than in group D at 24 hours after surgery ($P < 0.05$) (Table 6).

Discussion

This study investigated the clinical efficacy and side effects of nalbuphine (0.07 mg/kg) and dexmedetomidine (0.5 μg/kg) for treating combined spinal-epidural anesthetic shivering in pregnant women after caesarean section. The incidence of shivering in the 120 women before treatment was 75.8%. Our study indicated the superiority of nalbuphine over dexmedetomidine for treating shivering as shown by a higher success rate, less time to shivering cessation, and less complications with nalbuphine.

This study showed that intravenous injection of nalbuphine effectively treated shivering, with a higher success rate and less time to cessation of shivering compared with dexmedetomidine. The incidence of bradycardia and excessive sedation after treatment with nalbuphine was low, while the incidence of bradycardia and excessive sedation after treatment with dexmedetomidine was high. This finding may be related to nalbuphine μ receptor antagonism and

Table 6. Comparison of postoperative plasma glucose and insulin levels.

	Plasma glucose		Insulin	
Group	Postpartum room	24 hours after surgery	Postpartum room	24 hours after surgery
Group C	5.70 ± 0.64	6.43 ± 0.53*	10.79 ± 1.26	12.01 ± 1.64*
Group N	5.69 ± 0.64	6.47 ± 0.51*#	10.42 ± 1.17	12.04 ± 1.82*#
Group D	5.70 ± 0.58	7.44 ± 0.62*	10.48 ± 1.14	11.00 ± 1.62*
P value	0.9948	<0.0001	0.3435	<0.0001

Data are mean ± standard deviation.
*$P<0.05$ compared with the time in the postpartum room; #$P<0.05$ compared with group D.
Comparisons for continuous data were made using one-way analysis of variance. Post hoc pairwise comparison was performed using the t-test or Kruskal–Wallis test for non-normally distributed variables and the Nemenyi test for normally distributed variables.
Group C: control group; group N: received an intravenous injection of nalbuphine 0.07 mg/kg; group D: received an intravenous injection of 0.5 μg/kg dexmedetomidine.

dexmedetomidine α2 adrenergic receptor activation. The sedative effect of nalbuphine, without respiratory depression, may be related to the sedative effect of dose-dependent opioids. This type of sedative effect can eliminate anxiety and reduce the pull reaction when clearing the abdominal cavity, which are beneficial for pregnant women with spinal anesthesia.

The mechanism of shivering during cesarean section is still not completely clear. This shivering may be due to vasodilation of the blocked segment, muscle relaxation, and weakening of the body's vasoconstriction reaction, resulting in a decrease in central chamber temperature. A decreased body temperature in the non-blocking area of the periphery may stimulate the body's temperature receptors to promote an increase in heat production by unblocking skeletal muscle contraction to maintain body temperature. Perioperative hypotension,[16] perioperative sympathetic excitation, and systemic pyrogen[17] are also important causes of shivering. In this study, the temperature of the operating room was kept within a certain range, and the anesthetic plane was controlled. During the operation, a warmer was used to control risk factors that affect the occurrence of shivering. There was no significant difference in the infusion volume of drugs among the three groups.

In the central nervous system, κ receptors are mainly distributed in the nucleus accumbens, the ventral tegmental area of the hypothalamus, the substantia nigra, the olfactory tubercle, and the amygdala. Activation of κ receptors can produce sensation of the skin stimulated by external temperature.[18] Nalbuphine has a high affinity for κ receptors. Nalbuphine plays an anti-shivering role in the hypothalamus. At the hypothalamic level, nalbuphine lowers the temperature regulation threshold for vasoconstriction and shivering because of the high density of α2 adeno-receptors in the hypothalamus.[17] Therefore, nalbuphine is effective in treating anesthetic shivering. Ashraf et al.[19] reported that intrathecal nalbuphine effectively prevented the occurrence of shivering after knee arthroscopic surgery that was performed under lumbar anesthesia. Nalbuphine is a "class B" opioid analgesic. In the American College of Obstetricians and Gynecologists' guide to clinical management of obstetricians, parenteral administration of labor analgesia, 10 to 20 mg is administered intravenously, subcutaneously, or intramuscularly for labor analgesia.[20] Wrench et al.[13] suggested that the minimum effective dose of

pethidine in treatment of shivering induced by spinal anesthesia was 0.35 mg/kg. The titer ratio of nalbuphine and pethidine is 1:5.[3] Therefore, a dose of 0.07 mg/kg nalbuphine was used to observe treatment of shivering in this study.

After an operation, the uterus needs massaging to eliminate uterine congestion. Uterine contractions can reduce postpartum bleeding, but they can also be a powerful irritant, which may induce a stress response and thus increase plasma glucose levels. The stress response is a non-specific defense response of the body, which is beneficial to recovery of the body, but an excessive stress response will cause damage to the body.[21] In this study, plasma glucose levels were significantly lower in group N than in group D. This finding indicated that the analgesic effect of nalbuphine was strong and lasted for a long time, which is consistent with a study conducted by Zhang et al.[22] The octanol–water distribution system of nalbuphine is P=1.5. Fat solubility of nalbuphine is low, which means that nalbuphine does not easily enter the central nervous system, thus greatly reducing adverse reactions.[23] Furthermore, after intravenous injection of nalbuphine postpartum, the content of nalbuphine in breast milk is small. Therefore, nalbuphine does not affect breastfeeding.[24]

Dexmedetomidine is a highly selective α2-receptor agonist with potential favorable physiological effects. Several studies have reported that dexmedetomidine is widely used in prevention of acute agitation and mechanical sedation.[25,26] Different studies have reported different concentrations of dexmedetomidine for relieving pain or shivering. Notably, dexmedetomidine is adopted to relieve pain by combination with other agonists. Park et al.[27] found that dexmedetomidine (0.2–0.7 μg/kg/hours) combined with remifentanil could reduce postoperative pain. Yu et al.[9] suggested that dexmedetomidine 0.05 μg/kg/hour is a better choice for anti-shivering, which is consistent with our study.

The main limitation of this study was the small sample size and that the study was only performed in a single center. Additionally, the observation index of the shivering scale was subjective, which depended on the difference between observers. At present, there is a lack of reliable and objective methods for determining shivering.

Conclusion

There is a significant effect of nalbuphine on preventing shivering after combined spinal-epidural anesthesia. Nalbuphine has a significantly better effect in reducing shivering and eliminating adverse reactions compared with dexmedetomidine, and this can improve the postoperative experience of pregnant women. Nalbuphine is an ideal drug for combined spinal-epidural anesthesia and can be used as the drug of choice for clinical prevention of shivering after combined spinal-epidural anesthesia.

Authors' contributions

JS wrote the first draft of manuscript; ZZ, LY, and LZ contributed to the conception and design of the research; GL and XW contributed to the experiments and analysis of the data; BS, XH, and YL contributed to the analysis and interpretation of the data. All authors critically revised the manuscript, and agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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