Intravenous injection of butorphanol prevents shivering of parturients undergoing cesarean section under epidural anesthesia: a randomized controlled trial

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Research article

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Abstract

Background The objective of this study was to assess the inhibitory effect of intravenous injection of butorphanol on the shivering in those parturients who underwent cesarean section (CS) under epidural anesthesia (EA). Methods 160 parturients planned for elective CS under EA were enrolled and finally 155 of them were included in this trial and randomly allocated to 4 groups. Before epidural anesthesia, parturients in Group A, B and C were respectively injected 7.5μg/kg, 5μg/kg and 2.5μg/kg butorphanol (100ug/ml) while none in Group D was given any drug. The incidence, duration and intensity of shivering, hemodynamic parameters of parturients, Apgar score of neonates, analysis of blood gas of umbilical cord and adverse events were recorded. Results The demographic characteristics of parturients of the four groups were similar. Compared with the control group (Group D), statistically significant attenuation of shivering was seen in the parturients of Group A and Group B. The incidence, intensity and duration of shivering of the Group A and Group B were all lower than those of the control group, but there was no statistical difference in the incidence, severity or duration time of shivering among groups receiving butorphanol. No patient displayed grade 4 shivering. There were no significant differences among the groups with mean arterial pressure (MAP), heart rate (HR), pulse oxygen saturation (SpO2), respiratory rate (RR) after administration of butorphanol. The incidences of most adverse effects such as nausea and vomiting, respiratory depression, and hypotension were also not seen statistical difference among the four groups. However, compared with other three groups, sedation parameter increased in Group A. Compared with Groups C and Group D, incidences of dizziness increased in Group A and Group B. There was no significant difference in Apgar score, PH, PCO2, PO2, HCO3- and lactic acid value among the newborns of the four groups. Conclusion The prophylactic administration of intravenous butorphanol 0.75μg/kg or 0.5μg/kg is effective on inhibiting shivering and can be safely used in parturients undergoing CS under EA, but 0.5μg/kg is more suitable because of less sedation. Dizziness of parturients should be monitored whichever dose is used.

Background

Shivering is a common distressing side effect in parturients undergoing cesarean section (CS) under epidural anaesthesia (EA). The incidence of shivering has been reported to be 36–85% (1, 2). The cause of shivering is still not completely understood but probably involves a number of mechanisms, including direct inhibition of hermoregulation by anesthetics, decreased metabolism, change in body heat distribution, reduction in body core temperature, patient exposure to cold environment, and body cavity exposure.

Shivering may cause discomfort and dissatisfaction in parturients undergoing cesarean section and it is also associated with some severe outcomes, such as increased blood pressure (BP), increased oxygen consumption and CO_2 production, lactic acid production (2), increased intraocular or intracranial pressure, increased wound pain and wound infection. Furthermore, it may also interfere with electrocardiographic and pulse oxymetric monitoring(3). Thus, effective prevention or treatment of shivering is desired.

In previous studies, different pharmacological and nonpharmacological techniques have been attempted to prevent and treat shivering. Pharmacologic interventions such as ketamine(4), tramadol(5), clonidine(5), sufentanil(6) and dexmedetomidine(7, 8) were effective in the treatment and prevention of shivering after anesthesia. These drugs have sedative properties and adverse effects including nausea, respiratory depression, dizziness, bradycardia, and hypotension. Anesthesiologists may be reluctant to administer these drugs before delivery because of unwanted effects on the mother and the fetus. Butorphanol is an opioid receptor agonist-antagonist which have been reported to be with less side effects of opioids such as nausea and vomiting as a shriving- treater. However, its effects on the shivering occurring during cesarean section and its'optimal dosage have not been reported. The objective of this study was to evaluate the effects of butorphanol on shivering in parturients who underwent CS under EA and to explore an appropriate dose.

Methods

2.1. Patient Selection.

This study was approved by the Ethics Committee of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (LCKY2018-56) and registered on http://www.chictr.org.cn: (registration number: ChiCTR1800019965). Every participant provided a written informed consent. Inclusion criteria included parturients planned for elective cesarean section under epidural anesthesia with 18 to 35 years of age, American Society of Anesthesiologists (ASA) physical status I or II, body mass index (BMI) 20 to 25 kg/m^2, 37 to 42 weeks of gestation age, and B-ultrasonography showed intrauterine single live fetus without umbilical cord around the neck, congenital malformation or other abnormal conditions. The exclusion criteria included parturients with history of liver dysfunction or kidney dysfunction or cardiopulmonary diseases, parturients with mental and neurological diseases, parturients with history of allergy, parturients who were complicated with hypertension and eclampsia and parturients who were not suitable for epidural anesthesia. Parturients would be dropped out if hemabate was used or the hemorrhage exceeded 500mL during delivery.

2.2. Anesthesia Procedure

The trial was conducted from December 15, 2018 to April 30, 2019 in the operation room of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. 160 parturients planned for elective CS under EA were enrolled and 158 of them were included and randomly allocated to 4 groups: Group A (n=39, receiving butorphanol 7.5ug/kg), Group B (n=40, receiving butorphanol 5.0ug/kg), Group C (n=40, receiving butorphanol 2.5ug/kg), and Group D (n=39, without butorphanol). None of the parturients was given any other premedications. Parturients were monitored by electrocardiography (ECG), noninvasive blood pressure (NIBP), and pulse oxygen saturation (SpO_2) every five minutes. The operating room temperature was maintained to 24~26°C and the humidity was maintained to 40%~60%.

Venous access was obtained in the upper limb with a 20G catheter. After the venous access was established, each group of parturients received corresponding intravenous medication: Group A (butorphanol 7.5ug/kg), Group B (butorphanol 5.0ug/kg), Group C (butorphanol 2.5ug/kg) and Group D (without butorphanol). After that, epidural puncture was performed at L2-L3, and 3 ml of 2% lidocaine was injected into the epidural catheter. If there was no sign of subarachnoid block after 5 minutes, 8~12ml of 0.75% ropivacaine and 0.2 mg (0.1 mg/ml) hydromorphone would be given for epidural anesthesia. Parturients' positions were adjusted to control the level of anesthesia at T6. Subsequently, parturients were placed in the supine position, and underwent segmental cesarean section.

A blinded observer was involved in the data collection. The incidence, intensity and duration of shivering were recorded as main parameters. Shivering severity was graded by Wrench standard scale (0 = no shivering; 1 = One or more of the following: piloerection, peripheral vasoconstriction, peripheral cyanosis with no other cause, but no muscle activity; 2 = visible muscular activity confined to one muscle group; 3 = visible muscular activity in more than one muscle group; 4 = muscular activity involving the whole body). Shivering was observed from the start of intravenous administration of butorphanol to two hours after surgery. Pulse oxygen saturation (SpO_2), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR) and sedation score (1=fully awake and oriented; 2=drowsy; 3=eyes closed, but open on command; 4=eyes closed, but open on physical stimulation; 5=eyes closed and unresponsive to physical stimulation.) were recorded at six points which were respectively before intravenous administration (T0), 5 min after intravenous administration (T1), 10 min after intravenous administration (T2), 15 min after intravenous administration (T3), 20 min after intravenous administration (T4) and 30 min after intravenous administration (T5). Apgar scores of newborn were recorded at 1 min, 5 min, and 10 min after delivery and cord blood were collected for blood gas analysis. Occurrence of nausea, vomiting, chest tightness, dyspnea, dizziness and other complications were also recorded during study.

Hypotension (systolic BP <90 mmHg or >30% drop from the baseline BP) was treated with intravenous ephedrine (5–10 mg). Decrease in the heart rate (<50 beats per min) was treated with intravenous atropine (0.3–0.5mg). Respiratory depression (pulse oxygen saturation <90% or >10% drop from the baseline) was treated with mask oxygen inhalation. Cephalic position was taken to flank side for parturient with nausea and vomiting, and intravenous administration of 8 mg ondansetron was given to those with severe vomiting. The amount of intravenous administration of any drug were recorded.

Any other important harms or unintended effects happened in any group would also be recorded.

2.3. Statistical Analysis.

Sample size estimates were done using PASS 11 software (PASS, Kaysville, UT, USA). In our pilot experiment, the incidence of shivering was 45% which decreased to 10% after the administration of intravenous butorphanol 7.5ug/kg. Assuming a <5% probability for a type I error, (i.e., significance level $\alpha=0.05$) and <20% for a type II error (i.e., accepting a null hypothesis when it is false, $\beta=0.20$), the required

sample size in each group was estimated to be 32. Allowing for 10% withdrawals, we recruited 40 parturients in each group.

Participants were randomly divided into four groups by using a computer generated random-number sequence. Wendong Lin generated the random allocation sequence. Shuying Fu enrolled participants and assigned participants to interventions and prepared the drugs. Liang Qi performed Epidural puncture and drugs administration. Bing Zhang and Mingpin Hu recorded and assessed the outcomes. Bing Zhang, Mingpin Hu and Participants were blinded after assignment to interventions.

The statistical analysis was performed using IBM SPSS Statistics 22.0 for Windows software (IBM Corp, Armonk, NY). Normal distribution of continuous varialbes data was tested by the Shapiro–Wilk test. Data pertaining to normally distributed continuous variables (age, weight, height etc.) were presented as a mean ± standardand deviation and analyzed using one-way ANOVA. Measurement data of non-normal distribution (BMI, gestational weeks etc.) were presented as a median (Q1, Q3) and analyzed with the Kruskal-Wallis H test. Categorical data were presented as numbers and proportions, and tested by the chi-square test or Fisher's exact test as appropriate. Continuous variables at different time points were compared by using repeated measures design analysis of variance. A value of $P<0.05$ was considered a statistically significant difference.

Results

160 parturients were enrolled in this study from December 15, 2018 to April 30, 2019 in the operation room of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. 2 of them were excluded before allocation due to declining to participate, 3 of them discontinued intervention due to failing epidural puncture or hemorrhage exceeding 500 ml, and 155 of them were finally included in the data analysis (as shown in Figure 1). There was no significant difference in parturients' demographic characteristics and total dose of ropivacaine among the groups ($P>0.05$, Table 1).

The incidences of shivering in Groups A, B, C and D were respectively 10.5% (4/38), 12.5% (5/40), 17.9% (7/39) and 34.2% (13/38) (Figure 2). Compared with Group D, the incidences of shivering were lower in Group A and Group B, as were the severity and duration of shivering ($P<0.05$, Figure 2, Figure 3 and Figure 4). However, there was no statistical difference in the incidences, severity or duration time of shivering among groups receiving butorphanol ($P>0.05$, Figure 2, Figure 3 and Figure 4). No patient displayed grade 4 shivering (Figure 3).

There was no significant difference in mean arterial pressure (MAP), heart rate (HR), pulse oxygen saturation (SpO_2), and respiratory rate (RR) after administration of intravenous butorphanol among the groups ($P>0.05$, Figure 5).

The incidences of most adverse effects such as nausea and vomiting, respiratory depression, and hypotension were not seen statistically different among the four groups ($P>0.05$, Table 2). However,

compared with other three groups, sedation scores significantly increased in Group A (P<0.01, Figure 6, A), while compared with Groups C and Group D, incidences of dizziness increased in Group A and Group B (P<0.05, Figure 6, B).

There was no significant difference in Apgar score、pH, PCO_2, PO_2, HCO_3^- and lactic acid value among the newborns of the four groups (P > 0.05、Table 3).

Discussion

Incidence of shivering of women undergoing epidural anesthesia for cesarean delivery is high. Many drugs have been reported for treatment or prevention of shivering: meperidine(9, 10), tramadol(11), pentazocine(12), clonidine(13), amitriptyline(14), ketamine(4) and so on. Butorphanol is an easily available opioid acting through κ and μ receptor. A few studies have denoted its anti-shivering properties(5, 15). In Bansal's study(5), the administration of intravenous butorphanol 1 mg used for treatment stopped 83% of shivering. In Rai's study(15) , the incidences of postoperative shivering were reduced from 60% to 15.5% in the general anesthesia group and from 43.3% to 10% in the spine anesthesia group by the administration of intravenous butorphanol 2 mg before anesthesia. In this study the incidences of shivering during cesarean section under epidural anesthesia were reduced from 34.2% to 10.5% and 12.5% respectively with the administration of intravenous butorphanol 7.5 μg/kg and 5 μg/kg before administering anesthesia, but there was no significant difference in the incidences of shivering between the groups receiving butorphanol. The intensity and duration time of shivering were also reduced by the administration of intravenous butorphanol 7.5 μg/kg and 5 μg/kg (as showed in Figure 3 and Figure 4). These results indicated that both 7.5μg/kg and 5μg/kg of intravenous butorphanol could well prevent perioperative shivering of parturients.

In this study, the incidence of shivering in Group D (control group) was 34.2%, lower than 36~85% which had been reported(1, 2). The relatively lower incidence of shivering in the control group of our study might be attributable to the additional preventive measures against the development of hypothermia such as the strict maintenance of room temperature and the restriction of cryogenic liquid infusion.

In the present study, there were no statistically significant differences in MAP, HR, RR and SPO_2 among the four groups (P>0.05, Figure 5), which indicated that the doses of butorphanol used in our study would not exert significant influence on maternal hemodynamics and respiratory function. There was also no statistically significant difference in the incidences of nausea and vomiting, respiratory depression and hypotension among the four groups. However, compared with other three groups, sedation parameter in Group A increased though with a range of little clinical significance(Figure 6, A). Besides, compared with Group C and D, more parturients in Group A and Group B experienced dizziness. This indicated that the administration of intravenous butorphanol would produce dose-dependent dizziness. However, those parturients undergoing dizziness only claimed the mild dizziness which did not increase the discomfort, which suggested that the doses of intravenous butorphanol administered pre-anesthesia in this study would be safe for parturients in cesarean section.

Opioids can move through the placenta and butorphanol is not excluded. However, Halder's research(16) showed that intramuscular injection of 1 mg butorphanol was safe for neonates in delivery anesthesia. In our study, Apgar scores, pH, PCO_2, PO_2, HCO_3^- and Lac value were similar in the four groups ($P > 0.05$, Table 3), which indicated that the administration of intravenous butorphanol at the all the doses of our study before anesthesia had no obvious effect on Apgar score and respiratory function of newborn.

Our study had some limitations. Firstly, due to the fact that the parturients in this study all had epidural anesthesia and underwent elective surgeries, our results may not be applicable to parturients undergoing spinal anesthesia or emergency surgery. Secondly, in our study, only three doses of 0.75μg/kg, 0.5μg/kg, and 0.25μg/kg were testified, which was lack of a dose–response experiment to determine the most optimal dose of butorphanol required for suppressing shivering without causing side effects. Further research can explore this.

Conclusions

In conclusion, the prophylactic administration of intravenous butorphanol 0.75μg/kg or 0.5μg/kg can both prevent shivering of parturients undergoing epidural anesthesia for cesarean section without obvious side effects, but 0.5μg/kg is more suitable because of less sedation; dizziness of parturients should be monitored whichever dose is used.

Abbreviations

EA: epidural anesthesia; CS: cesarean section; MAP: mean arterial pressure; HR: heart rate; SpO_2: pulse oxygen saturation; RR: respiratory rate; BP: blood pressure; ASA: American Society of Anesthesiologists; BMI: body mass index; ECG: electrocardiography; NIBP: noninvasive blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; ANOVA: analysis of variance; SPSS: Statistical Product for Social Sciences.

Declarations

7.1 Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (LCKY2018-56) and registered on http://www.chictr.org.cn: (registration number: ChiCTR1800019965, December 10, 2018). Every patient who participated in the study provided her written informed consent.

7.2 Consent for publication

Not applicable.

7.3 Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its additional files.

7.4 Competing interests

The authors declare that they have no competing interests.

7.5 Funding

Not applicable.

7.6 Authors' contributions

SF designed and partly performed the trial and wrote the manuscript.

LQ performed the Epidural puncture and drugs administration.

BZ and MH recorded and assessed the outcomes.

XL assisted with data analysis.

JL and QL guided the implementation of the experiment.

WL assisted in the design of the trial, analyzed the data and revised the manuscript.

All authors read and approved the final manuscript.

7.7 Acknowledgements

Not applicable.

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Tables

Table 1. Demographic characteristics and total dose of ropivacaine

Group	A (n=38)	B (n=40)	C (n=39)	D (n=38)	*P* value
Age (year)[a]	33.9±5.3	32.5±4.6	32.3±4.5	33.0±4.9	0.482
Height (cm)[a]	158.5±3.7	158.3±5.9	158.9±4.3	159.6±3.8	0.613
Weight (kg)[a]	64.7±6.4	66.9±7.4	67.9±7.0	68.9±7.5	0.058
BMI (kg.m-2)[b]	25.2 (23, 27.3)	27.2 (24.6, 28)	27 (24.6, 29.2)	27 (24.9, 29.4)	0.067
Gestational age (week)[b]	38 (37.8, 39)	38 (38, 39)	38 (38, 38)	38 (38, 39)	0.412
Total dose of ropivacaine (0.75%, ml)[b]	8 (8,10)	8 (8,10)	8 (8,10)	8 (8,10)	0.595

[a] Data were reported as Means ± SD. One-way analysis of variance (ANOVA) was used for comparison. [b] Data were reported as Median (Q1, Q3). Kruskal-Wallis H test was used for comparison.

Table 2. Adverse effects (except dizziness) in four groups

Group	A (n=38)	B (n=40)	C (n=39)	D (n=38)	*P* value
Nausea or vomiting (n(%))	0 (0)	2 (5)	1 (2.6)	1 (2.6)	0.585
Respiratory depression (n(%))	0 (0)	1 (2.5)	0 (0)	2 (5.3)	0.283
Hypotension (n(%))	9 (23.7)	10 (25)	10 (25.6)	8 (21.1)	0.967

Data were reported as numbers (proportions). Chi-square test was used for comparison.

Table 3 Apgar scores and umbilical cord blood gas analyses of four groups

Group		A	B	C	D	*P* value
pH		7.35 (7.34, 7.36)	7.35 (7.34, 7.36)	7.35 (7.33, 7.36)	7.35 (7.33, 7.36)	0.91
PCO_2		41.5 (39.2, 44,9)	41.4 (39.6, 44.4)	42.0 (39.5, 44.8)	41.0 (38.9, 44.7)	0.422
PO_2		32.0 (24.9, 38.0)	29.0 (25.0, 31.2)	26.8 (23.0, 32.1)	30.3 (24.5, 33.9)	0.085
HCO_3^-		22.0 (20.8, 22.8)	22.2 (21.5, 23.1)	22.5 (21.4, 23.5)	22.1 (21.2, 23.7)	0.561
Lac value		2 (1.7, 2.3)	1.8 (1.6, 2)	1.8 (1.7, 2.2)	1.9 (1.6, 2.1)	0.074
Apgar	1 min	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	
	5 min	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	0.424
	10 min	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	

Data were reported as Median (Q1, Q3). Kruskal-Wallis H test was used for comparison.

Figures

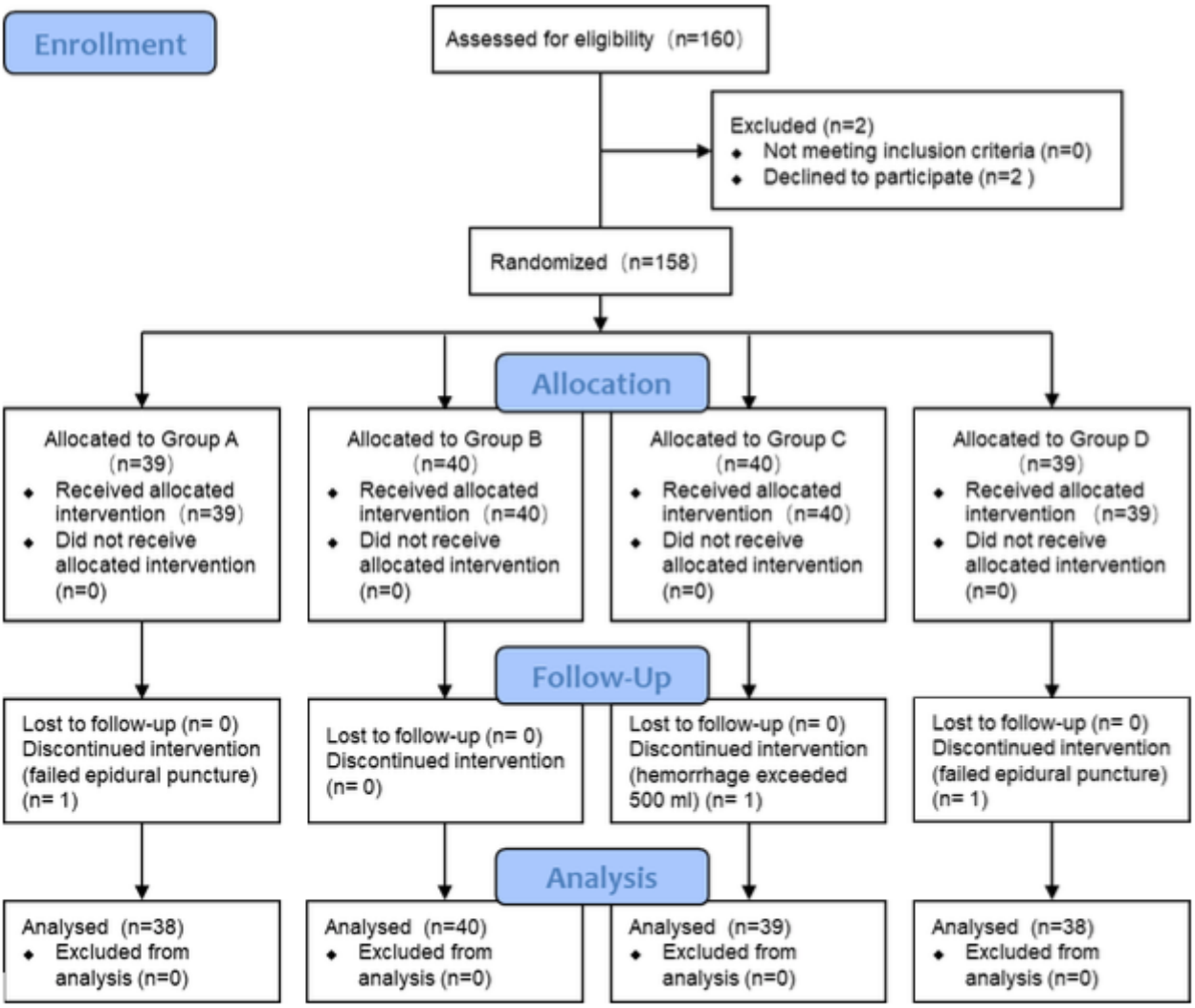

Figure 1

Flow of participants through the study.

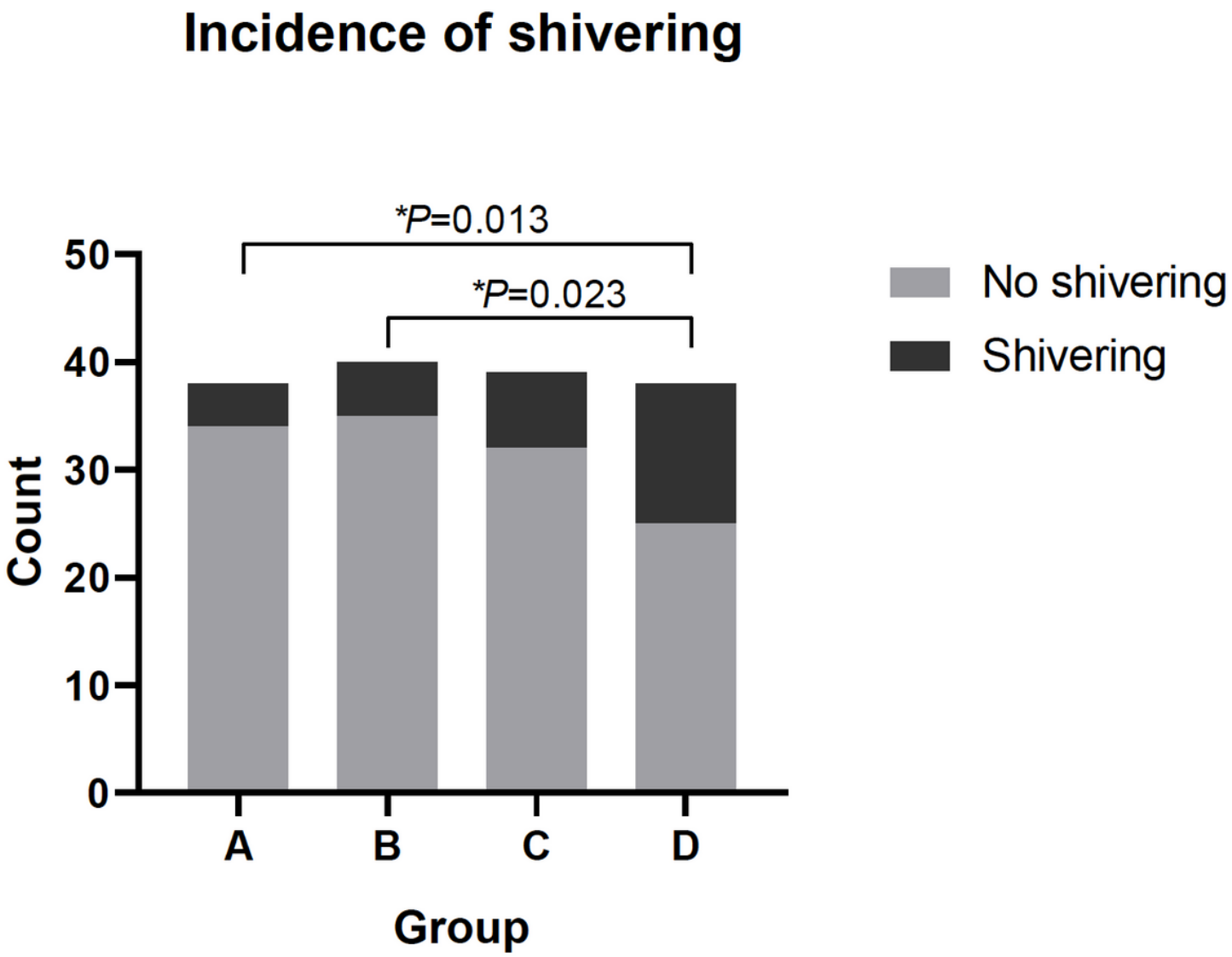

Figure 2

Incidence of shivering of four groups * P<0.05.

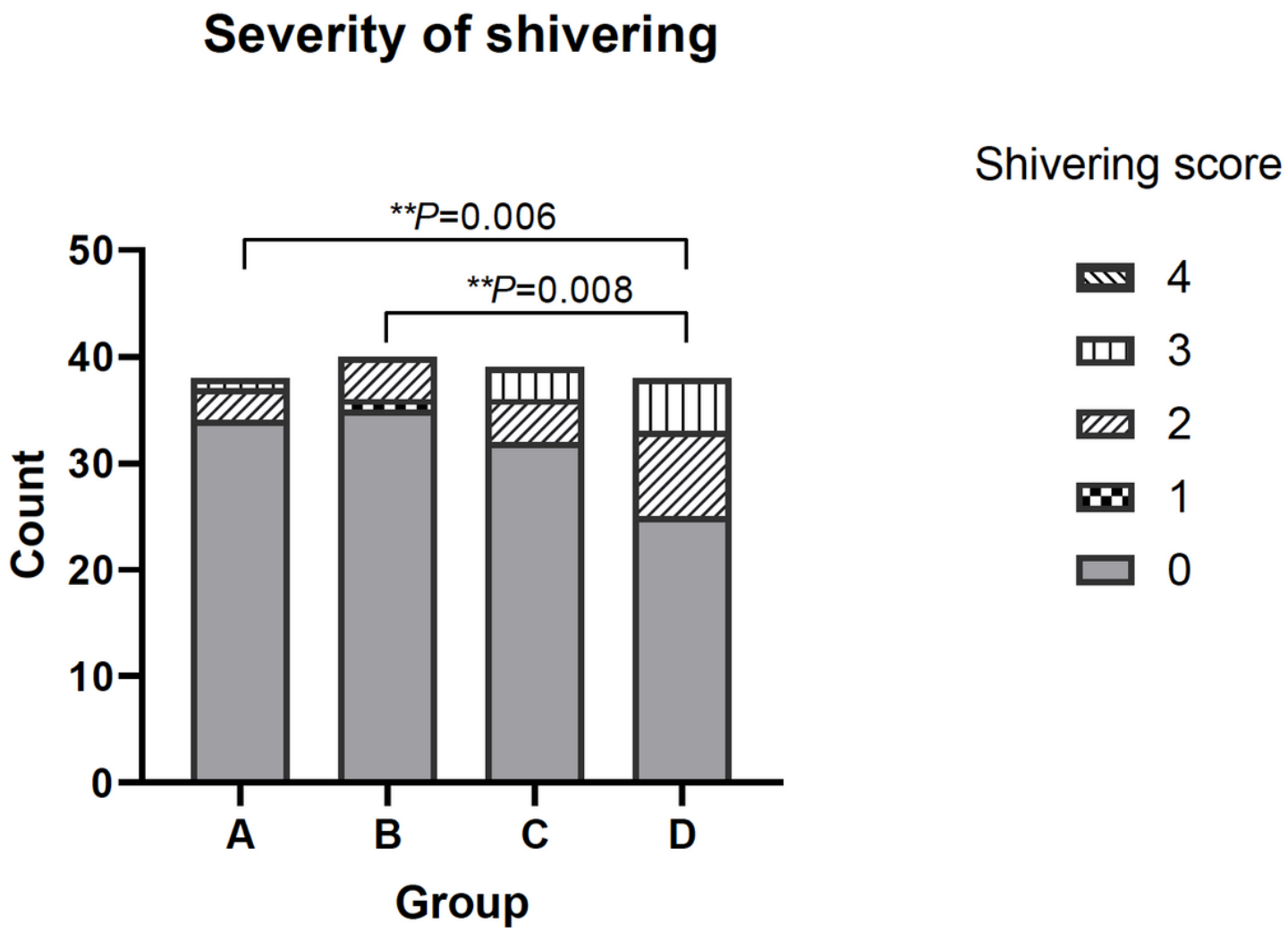

Figure 3

Severity of shivering of four groups **P<0.01.

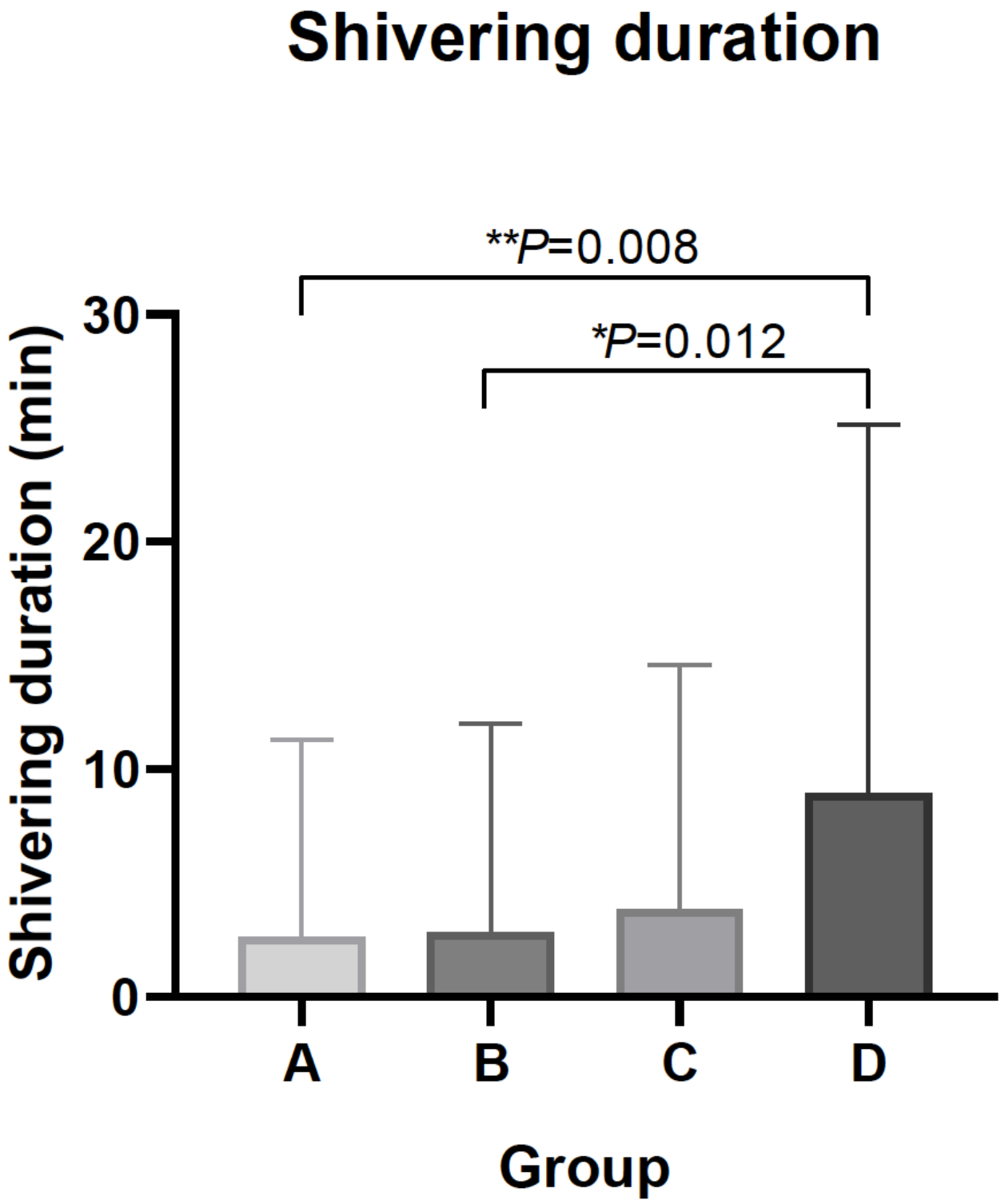

Figure 4

Shivering duration of four groups * P<0.05 **P<0.01.

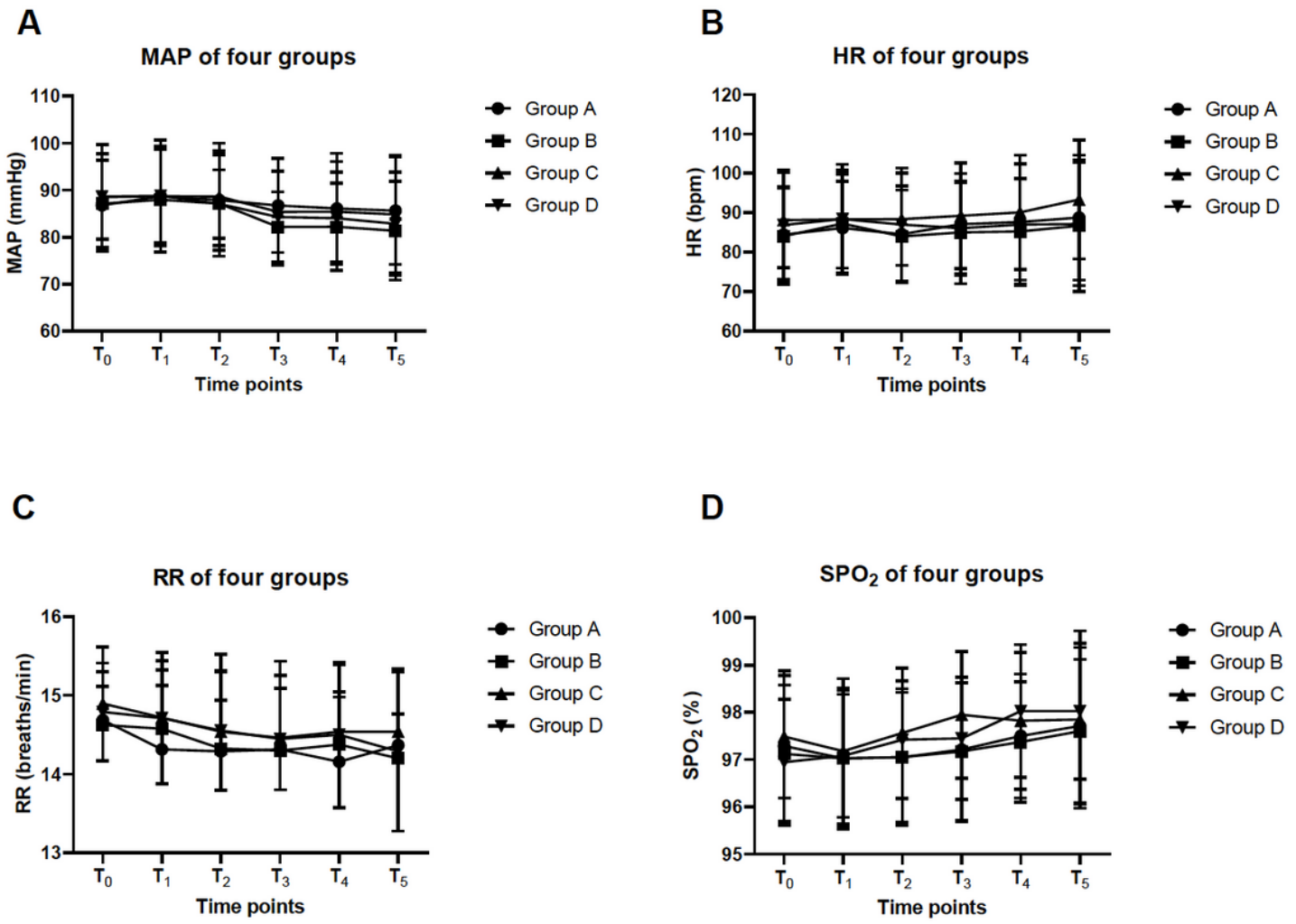

Figure 5

MAP, HR, RR and SPO2 during the study showed no significant differences between four groups. A. MAP of four groups；B. HR of four groups；C. RR of four groups；D. SPO2 of four groups.

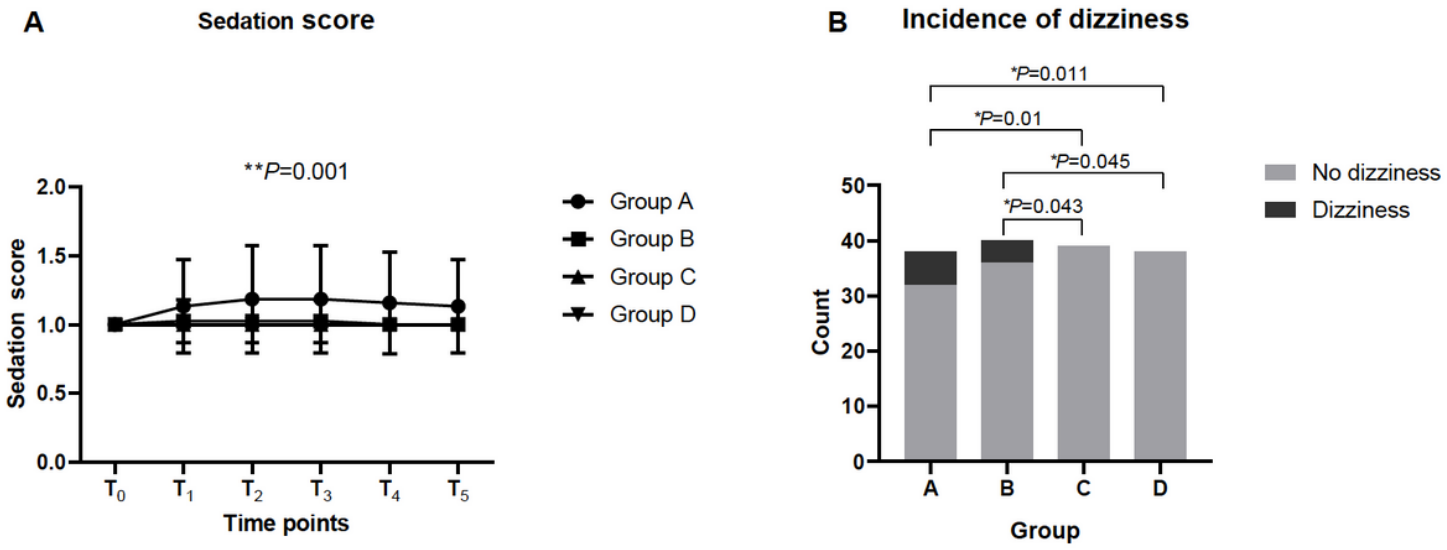

Figure 6

Sedation scores and incidences of dizziness of the four groups during the study A. Sedation scores of four groups Sedation scores significantly increased in group A compared with groups B, C, and D. **P<0.01. B. Incidences of dizziness of four groups Compared with group C and group D, incidences of dizziness in group A and group B significantly increased. *P<0.05.

Supplementary Files

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