S-Ketamine As An Adjuvant in Patient-controlled Intravenous Analgesia for Prevention of Postpartum Depression: A Randomized Controlled Trial

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Research Article

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Abstract

(1) Background: Postpartum depression (PPD) is a common complication after cesarean section. Recent studies have shown that intravenous S-ketamine during surgery could be effective in preventing PPD. However, no evidence shows S-ketamine used in patient-controlled intravenous analgesia (PCIA) could reduce the incidence of PPD. Our aim was to explore the effect of S-ketamine as an adjuvant in patient-controlled intravenous analgesia (PCIA) for prevention of postpartum depression.

(2) Methods: In a single center, 375 parturients scheduled to undergo cesarean section were recruited and randomly assigned to two groups: Control group (C group) or S-ketamine group (S group). Parturients in both groups received PCIA, the formula of Group C: sufentanil 2 µg/kg + tropisetron 10 mg, S group was the same as C group except 0.5mg/kg S-ketamine. The primary outcome was the incidence of PPD measured by the Edinburgh Postnatal Depression Scale (EPDS) after surgery. The secondary outcomes were EPDS scores, Visual analogue scale (VAS) scores, and Ramsay Sedation Scale (RSS) scores, and incidence of related adverse events.

(3) Results: A total of 275 puerpera were finally included and randomly assigned to two groups. The incidence of depression at postoperative 3, 14, 28days in C group and S group were 17.6%vs8.2%, $P<0.05$; 24.2%vs9.8%, $P<0.05$, and 19.0%vs 17.2%, $P=0.76$, respectively). As for EPDS scores, C group and S group at 3,14, and 28 days after cesarean were 7.65 ± 3.14 vs 6.00 ± 2.47 , $p<0.05$, 7.62 ± 3.14 vs 6.38 ± 2.67 , $p<0.05$, and 7.35 ± 3.17 vs 6.90 ± 2.78 , $p=0.15$, respectively. Adverse events such as headache and nausea were 3.3% vs 4.1%, $p=0.755$; 5.9%vs8.2%, $p=0.481$.

(4) Conclusions: 0.01mg/kg/h S-ketamine as an adjuvant in patient-controlled intravenous analgesia can significantly reduce the incidence of postpartum depression within 14 days and relieve postoperative pain within 48h after cesarean section, without increasing the incidence of adverse reactions.

Trial registration: ChiCTR, ChiCTR2100050263 retrospectively registered. Registered 24/08/2021.

Introduction

Postpartum depression (PPD) is a common psychosocial disorder that can have adversely affect the life of the mother, as well as the baby and family[1]. It has been reported the incidence of PPD is 1%-52.1% in China[2, 3], and severe depression that requires hospitalization is more likely to occur after childbirth than in women at any other time[4], because childbirth is a powerful trigger for mania and psychosis, and episodes at this period could substantially increase the risk of suicide, which is a leading cause of maternal death[5]. Therefore, reducing the occurrence of puerperal getting PPD is necessary.

In obvious studies, ketamine has been proved to be a powerful drug to release depression and reduce suicidal tendency in depressed patients[1, 6, 7]. Some reports have proved that the intravenous injection of ketamine during cesarean section could be effective in preventing postpartum depression until 3 days to 6 weeks[1, 3, 8]. S-ketamine, the dextral resolution of ketamine, its anesthetic effect is twice as

effective as the racemic mixture and about three times as potent as (R)-ketamine[9–13]. Besides, as the side effects of ketamine are dose-dependent, S-ketamine has a lower incidence of adverse events than ketamine when we aimed to arrive at the same sub-anesthetic effect[14]. So we presume that S-ketamine used for PCIA may be a good choice as it can continuedly to infuse for 2 days at about 0.01mg/kg/h. Therefore, we hypothesized that S-ketamine as an adjuvant in patient-controlled intravenous analgesia can prevent postpartum depression.

Methods

Study design

The research scheme was approved by the Ethics Committee of Henan Provincial people's Hospital ([2019] 53), Henan, China, and registered in the China Clinical trial Registration Center, registration number:ChiCTR2100050263, (24/08/2021,retroactive registration). All subjects received informed written consent.

Participants

Parturients from 1 September 2019 to 15 July 2020 in Henan Provincial People's Hospital were enrolled. Eligibility criteria included the following: (1) undergoing cesarean delivery in our hospital, (2) the age of puerperal is ≥ 18 and ≤ 45 , (3) the birth age is ≥ 36 and ≤ 42 weeks, (4) BMI 17-36kg/m², and (5) ASA grade ranged I-II; Exclusion criteria included: (1) The puerperal has experienced depression and has been diagnosed as depression by a psychiatrist before, (2) the pregnant has experienced domestic violence before, (3) the pregnant with a serious obstetric complication or serious foundational diseases, (4) the newborn has serious genetic or congenital diseases, and (5) multiple pregnancies.

Randomization and blinding

Parturients were randomly assigned in a 1:1 ratio to S-group or C-group using SPSS 25.0. Parturients signed informed consent forms by themselves on the day of undergoing cesarean. Anesthesiologists, parturients, follow-up investigators were blinded throughout the study period. Staff who distribute PCIA generated the random allocation sequence, knew the group assignment of patients.

Procedures

All parturients underwent spinal anesthesia at L3-L4 or L2-L3 level and received patient-controlled anesthesia after surgery. The spinal anesthesia solution was 1% ropivacaine 2mL+10% glucose 1 mL, anesthesiologist controlled at 1 ml/5 s to arrive block level up to T4–T6.. At the end of surgery, all parturients would receive NSAIDs drug (propacetamol 2.0g intravenous drip) and transversus abdominis plane (TAP) nerve block at ultrasound-guided for preemptive analgesia. Parturients in the C group received a PCIA with sufentanil 2µg/kg and tropisetron 10 mg while parturients in the S group received S-ketamine 0.5 mg/kg, sufentanil 2µg/kg, and tropisetron 10 mg. The volume of the PCIA in both groups is

100 mL, which can support 48h's anesthesia with the infusion of 2mL/h, PCIA doses 2ml/h, maximum dose 10ml/h, blocked time is 15min.

Parturients were followed up by investigators at 4h (T1), 8h (T2), 12h (T3), 24h (T4), 48h (T5) after cesarean, and 3, 14, 28 days postpartum. The VAS and RSS scores were administered at 4h, 8h, 12h, 24h, 48h after cesarean. EPDS was administered on days 3, 14, 28 postoperatively. The EPDS contains ten questions with four sub-answers correspondingly and 0-3 points for each answer, the total score is 0-30. In our study, EPDS score ≥ 10 was considered to diagnose postpartum depression.

Any discomfort (headache, nausea, dizziness, drowsiness, and vomit, et al) will be recorded during they use PCIA.

The scores of EPDS were tested before surgery, 3 days, 14 days, and 28 days after surgery. On the days of 3, 14, 28 days after cesarean, parturients were contacted by phone or WeChat to complete EPDS by investigators.

Outcome measures

The incidence of PPD is our primary outcome. The secondary outcomes were scores of EPDS at days of 3, 14, 28 days after cesarean section. RSS scale and VAS scores were assessed at 4h(T1), 8h(T2), 12h(T3), 24h(T4), and 48h(T5) postpartum.

Adverse events including headache, nausea, dizziness, drowsiness and vomit were recorded during parturients using PCIA.

Sample size and statistical analysis

According to previous studies[2, 3], when the EPDS score ≥ 10 was used as the detection threshold of postpartum depression, the prevalence rate of postpartum depression in China is 28.2%. We assumed that ketamine used for PCIA will reduce postpartum depression to 15%; with 80% statistical power, $\alpha = 0.05$ for two-tailed tests, PASS 15.0 software yielded a sample size of 300 (150 parturients in each study arm); assuming a 20% drop-out rate, the sample size was finally established at 375.

Continuous variables are presented as the mean $\pm$ standard deviation or as the median (min and max range); t-test or Mann–Whitney U test was performed for between-group comparisons. Categorical variables are presented as percentages; these data were compared using X² test or Fisher's exact test. The SPSS 25.0 software was used for the statistical analysis. A value of $P < 0.05$ was considered statistically significant for two-tailed tests.

Results

During the time of 1 September 2019 to 15 July 2020, a total of 451 parturients were eligible, 71 parturients chose vaginal delivery for various causes. So 380 were enrolled in this trial, and 53 parturients refused to continuously participate in this study after cesarean section. Thus, 327 parturients were

ultimately enrolled in this trial. During 28 days' follow-up, 52 subjects were lost. So, 275 parturients were finally included in analyzed (Figure 1).

Baseline characteristics

The baseline characteristics of subjects were listed in Table 1 and were well balanced between the S group and C group.

Table 1
Characteristics of the parturients between two groups

	C group(n=153)	S group(n=122)	P-value
Age, years	31.85±4.16	31.64±3.93	0.71
ASA physical status, $\square/\square$	39/114	31/91	1.0
BMI, kg/m ²	26.89±2.58	27.08±2.95	0.63
Time of surgery, min	51.59±11.07	53.60±9.99	0.31
Blood loss, ml	301.83±98.47	320.90±121.26	0.73
EPDS score before surgery	6.54±2.35	6.72±2.25	0.48
Primipara, yes/no	114/39	84/38	0.30
Education background			0.19
Primary school	3	2	
Secondary school	26	10	
High school	48	41	
University	76	69	
Planned pregnancy, yes/no	137/16	108/14	0.34
Gender, boys/girls	81/72	77/45	0.66
Infant feeding ¹			0.12
Maternal	105	97	
Mixed	34	17	
Artificial	14	8	
Major family accident ^{1,2}	1	2	0.59
¹ We record these data until 28 days after cesarean section, ² Unemployment, lost families, etc.			

Primary outcome

For the primary outcome of our study, the occurrence of depression between two groups, the S group was significantly less than the C group at 3 days and 14 days after cesarean ((17.6%vs8.2%, $P<0.05$;24.2%vs9.8%, $P<0.05$, respectively), but no difference at 28 days (19.0%vs17.2, $P>0.05$). (Figure 2).

Secondary outcome

The secondary outcome, EPDS scores were similar and defined as no depression between two groups before cesarean (6.54 ± 2.35 vs 6.72 ± 2.25 , $P=0.508$). However, we found significant differences in the score of EPDS at the time of 3 days (7.65 ± 3.14 vs 6.00 ± 2.47 , $p<0.001$), 14 days (7.62 ± 3.14 vs 6.38 ± 2.67 , $p<0.001$) after cesarean. 28 days of EPDS scores have assessed no difference between the two groups (7.35 ± 3.17 vs 6.90 ± 2.78 , $p=0.217$). (Figure 3)

As for VAS scores of T1, T2, T3, T4, there were significant differences between the two groups at various times, furthermore, the S group was always less than the C group. (Figure 4a) RSS scores were recorded at the time of 4h(T1),8h(T2),12h(T3),24h(T4) postpartum, and they were similar except T4 (1.99 ± 0.14 vs 2.05 ± 0.22 , $p=0.015$) (Figure 4b). The occurrence of adverse events between the two groups are no different (Table 2)

Table 2
Adverse events during using PCIA

Adverse events	C-group (%)	S-group (%)	Total (%)	P value
Headache	5(3.3)	5(4.1)	10(3.6)	0.755
Nausea	9(5.9)	10(8.2)	19(6.9)	0.481
Dizzy	14(9.2)	15(12.3)	29(10.5)	0.434
Drowsiness	10(6.5)	13(10.7)	23(8.4)	0.274
Vomit	9(5.9)	7(5.7)	16(5.8)	0.585

Discussion

In this trial, we found that 0.01mg/kg/h S-ketamine used in PCIA for women who undergo cesarean can reduce the incidence of postpartum depression and scores of EPDS within 14 days effectively, simultaneously not increasing side reaction. Besides, PPD was increased along with time flowed within 1 month in both groups we observed, which is consistent with the previous studies[1, 15, 16].

Some reports have shown ketamine's short and rapid effect on reducing parturient's depression symptoms[12, 17, 18]. However, these reports differed from our study to some extent. In a study by Yao. J et al[8], healthy women scheduled for cesarean delivery were received intravenous ketamine 0.25 mg/kg intraoperative but not postoperative. interestingly, their results showed that PPD was effectively reduced at 1 week postpartum, instead of at 2 weeks and 4 weeks. Besides, the prevalence of adverse events such

as headache, hallucination, and dizziness were higher in the ketamine group during the operation. The reason why their results were inconsistent with ours may be because it was only using ketamine once in subanesthetic dose instead of continuing intravenous administration. Our study chose a continuous infusion of 0.01mg/kg/h ketamine used in PCIA, which can last a long time to prevent or therapy depression. The following methodological differences between the current trial and Yao's trial might partially explain the discrepant findings: intervention differ, compliance with trial protocols, population local distribution, rigor in depression ascertainment.

EPDS scores are usually used to screen for postpartum depression when scores are ≥ 10 [19, 20], and it is suggested that depression be tested or diagnosed before 6 weeks postpartum[21–25]. The questionnaire we used was the Chinese version of EPDS, which was proved to be well-validated to Chinese women. In a previous study[16], parturients who were given ketamine 0.5 mg/kg at 10 min after childbirth, and 160 mg ketamine in PCIA postoperative, found that it effectively reduced postpartum depression and postpartum blue in 4 days after cesarean. It can support our result that the incidence of PPD in the S group reduced significantly at 3 days and 14 days postoperatively to a certain extent.

Recent studies have demonstrated that a low dose of ketamine can reduce the incidence of anesthetic side reactions[14]. A review recently advised that parturients outside the perioperative setting could use ketamine as an analgesic or sedative to mitigate mood and depression[7], which was corresponded to our results. In our study, the VAS score was significantly lower in S-group during they used PCIA. The incidence of headache, nausea, dizziness, drowsiness, and vomit decreased to a certain extent, though no significant difference was found.

Earlier research showed that single doses of intravenous S-ketamine or ketamine use during cesarean section delivery may not affect the breastfed infant or lactation[2]. The dose of S-ketamine we administered is lower than sub-anesthetic, so we believe 0.5mg/Kg S-ketamine diluted in 100ml saline intravenous lasts 48h is safe for both mother and infant[26, 27].

This trial also has some limitations. First, the trial sample size is not big enough, and the population is residents. Maybe we should conduct multicenter studies to enroll more subjects in future studies. Second, in studies of Salloum et al, time to relapse depression after successful treatment of ketamine appears to follow a dose-response relationship, where higher dosage leads to increased time to relapse[28, 29]. We chose the dose of S-ketamine in PCIA as 0.5mg/Kg, so we don't know if more or fewer doses could show a better effect on preventing postpartum depression. Future research could explore a better dose of S-ketamine as an adjuvant in PCIA, which to guide doctors to prevent PPD. Third, we followed up with parturients until 28 days postpartum, because of more mixed factors such as stressful life events, poor social support, poor marital relationship, personal vulnerability, and low socioeconomic status[2, 15, 30–35], which could influence the future incidence of PPD along with time flow. By the way, we recorded these elements in 28 days after cesarean section and there was consistency between the two groups. Maybe those factors could influence our primary outcomes but we did not record them. Future studies should consider involving these elements in baseline characteristics.

Conclusions

In conclusion, 0.01mg/kg/h S-ketamine as an adjuvant in patient-controlled intravenous analgesia can significantly reduce the incidence of postpartum depression within 14 days and relieve postoperative pain within 48h after cesarean section, without increasing the incidence of adverse reactions. This finding supports the efficiency and safety of S-ketamine used in PCIA to reduce postpartum depression. Future researches should include a larger number of parturients in similar studies, and the interactional relationships between serologic indexes and precipitating risk factors for postpartum depression should be explored.

Abbreviations

ASA: American society of anesthesiology; EPDS: Edinburgh Postnatal Depression Scale; PCIA: patient-controlled Intravenous analgesia; PPD: Postpartum depression; RSS: Ramsay Sedation Scale; VAS: Visual Analogue Scale

Declarations

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Author Contributions

Conceptualization—Yaqian Han and Pule Li; methodology—Mengrong Miao; formal analysis—Yuan Tao; writing—original draft preparation—Yaqian Han; writing—review and editing—Pule Li and Jiaqiang Zhang; visualization—Xia Kang; project administration—Jiaqiang Zhang; funding acquisition—Jiaqiang Zhang. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets generated during the current study are not publicly available due the regulation of data management of Henan Provincial People's Hospital, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Henan Provincial People's Hospital Ethics Committee ([2019]53), Henan, China, and registered in the Chinese Clinical Trial Registry (registration no. ChiCTR2100050263 retrospectively registered) (also see <https://www.chictr.org.cn/showproj.aspx?proj=129088>). Informed written consent was obtained from all subjects. Data are available on reasonable request. Data will be available (following deidentification of the participant data) on request via email to the corresponding author.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee Henan Provincial People's Hospital Ethics Committee ([2019]53), approval date: August 21, 2019). All women involved in this study filled out informed consent and data treatment forms to enter the study, in accordance with the ethical standards of the Ethics Committee.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not Applicable.

Competing interest

The authors declare that they have no competing interests.

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Figures

Figure 1

<p> Flow Diagram</p>

Figure 2

The incidence of PPD after cesarean section

*: $P \leq 0.05$; Day 3 Day 14, and Day 21 refers to 3 days, 14 days, and 28 days after surgery.

Figure 3

EPDS scores at different time

P value ≤ 0.05 ; Day 0, Day 3, Day 14, and Day 28 refers to before cesarean, 3 days, 14 days, and 28 days after cesarean.

Figure 4

VAS(4a) and RSS(4b) scores at different times during using PCIA.

**: $P \leq 0.05$, T1, T2, T3, T4, and T5 means 4h, 8h, 12h, 24h, and 48h after they begin using PCIA.