



Prophylactic use of ketamine reduces postpartum depression in Chinese women undergoing cesarean section[☆]



Ma Jia-Hui^{a,1}, Wang Sai-Ying^{a,b,1}, Yu He-Ya^a, Li Dan-Yang^a, Luo Shi-Chao^a, Zheng Shan-Shan^a, Wan Li-Fei^c, Duan Kai-Ming^{a,*}

^a Department of Anesthesiology, Third Xiangya Hospital of Central South University, Changsha 410013, PR China

^b Hunan Key Laboratory of Pharmacogenetics, Institute of Clinical Pharmacology, Central South University, Changsha 410078, PR China

^c People's Hospital of Ningxiang City, Ningxiang 410600, PR China

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ABSTRACT

This study aimed to explore the effect of prophylactic ketamine administration on postpartum depression in Chinese woman undergoing cesarean section. This randomized controlled study included 654 Chinese women undergoing cesarean section. At 10 min after child birth, patients in the ketamine group were given 0.5 mg/kg ketamine, whereas patients in the control group received standard postpartum care. At the end of operation, all patients were armed with a patient-controlled intravenous analgesia device. The primary outcome was the prevalence of postpartum depression (PPD), as assessed by the Edinburgh Postnatal Depression Scale (EPDS), and the secondary outcomes included the safety assessment and the Numerical Rating Scale (NRS) of post-operative pain. The prevalence of postpartum blues and postpartum depression were significantly lower in the ketamine group than in the control group. Logistic analysis showed that ketamine administration protected against postpartum depression, and PPD-associated risk factors included stress during pregnancy, antenatal depressive symptom and antenatal suicidal ideation. In addition, the antidepressive effect of prophylactic ketamine was stronger in mothers with a history of moderate stress during pregnancy, antenatal depressive symptom and antenatal suicidal ideation. Our findings suggest that ketamine functions as a prophylactic agent against PPD.

1. Introduction

Postpartum depression (PPD) is a common psychiatric disorder that occur in the postpartum period. It is estimated that PPD occurs in approximately 10–20% of mothers (Hansotte et al., 2017; Meltzer-Brody et al., 2018), irrespective of culture or race. PPD severely impairs maternal life quality, and (Lindahl et al., 2005) even accounts for 20% postpartum deaths. PPD also negatively affects family relationships, including marital discord, impaired mother-infant bonding, and poorer physiological and psychological health of the offspring (Farias-Antunez et al., 2018; Plant et al., 2015; Werner et al., 2015). However, there is no effective prophylactic treatment for PPD.

Some lines of evidence have shown that the glutamatergic system plays an important role in depressive disorder, as well as in postpartum

psychological disorders (Beneyto et al., 2007; Meador-Woodruff et al., 2001). PPD patients exhibit altered glutamate concentrations in dorsolateral prefrontal, similarly to other subtypes of (Rosa et al., 2017) depressive disorders. We have previously found that a polymorphism in the NR2B gene is associated with PPD, suggesting that the glutamatergic N-methyl-d-aspartate (NMDA) receptor contributes topped. Stress is a primary risk factor for most mood disorders, including PTSD, depression and anxiety. Preclinical studies have showed that glutamate signaling plays a prominent role in chronic stress-induced HPA axis activation in many brain regions, and alterations in the glutamatergic system also drive the consequences of HPA axis activation (Berman et al., 2000). HPA axis activation induced by stress also contributes to the pathophysiology of postpartum psychiatric disorders. In addition, it has been reported that PPD is significant correlated with the

[☆]Sai-Ying Wang designed the trial. Shi-Chao Luo and Li-Fei Wan was responsible for the group allocation and anesthesia. Jia-Hui Ma, Dan-Yang Li and Shan-Shan Zheng followed up the patients. He-Ya Yu analyzed data. Jia-Hui Ma wrote the first draft of the manuscript. Sai-Ying Wang and Kai-Ming Duan revised the manuscript. All authors contributed to and have approved the final manuscript.

* Corresponding author.

E-mail address: duankaiming@126.com (K.-M. Duan).

¹ Jia-Hui Ma and Sai-Ying Wang contributed equally to this work.

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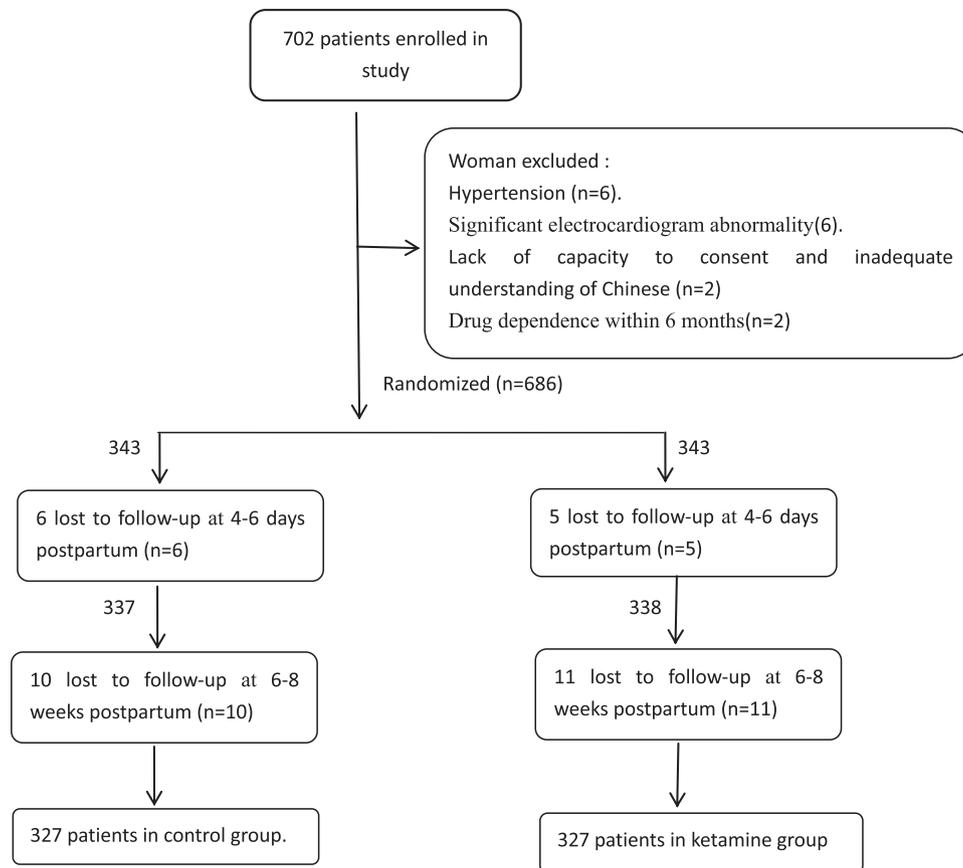


Fig. 1. Study flow chart.

glutamate metabolism, and the decreased HPA axis responsiveness in PPD was linked to lower concentrations of metabolites of the glutamatergic complex in the anterior cingulate gyrus (de Rezende et al., 2018).

Ketamine, a non-competitive antagonist of the NMDA receptor, has been used for many decades as an anesthetic during the surgery such as caesarean section. Numerous studies have demonstrated that ketamine produces the antidepressant effect in patients with depressive disorders (Lapidus et al., 2014; Murrrough et al., 2013; Vande Voort et al., 2016). At the recommended dosage of ketamine (0.5 mg/kg i.v), ketamine even decreases suicidal thoughts in bipolar disorder patients (Grunebaum et al., 2017; Murrrough et al., 2015). Ketamine produces the antidepressant effects by blocking the NMDA receptor and subsequently activates the mammalian target of rapamycin (mTOR) and inhibits the eukaryotic elongation factor 2 (eEF2) signaling pathways. Fast activation of mTOR signaling results in an elevation of synaptic spine numbers and function in the PFC, whereas eEF2 phosphorylation can desuppress the translation of brain-derived neurotrophic factor (Autry et al., 2011; Li et al., 2010). Ketamine also decreases glycogen synthase kinase-3 (GSK-3) and inhibits the kynurenine pathway activity, suggesting that ketamine may link to decreased levels of pro-inflammatory cytokines (Liu et al., 2013).

Ketamine has also been found to act as a prophylactic agent against stress-related disorders (Musazzi et al., 2018). Preclinically, a single dose of ketamine protects against depression-like behavior, in mice with chronic social defeat model and the learned helplessness and chronic corticosterone models (Brachman et al., 2016). A randomized trial has showed that the ketamine rapidly reduces the severity of chronic post-traumatic stress disorder (PTSD) (Feder et al., 2014). Musazzi and colleagues believe that ketamine may exert a prophylactic action in stress-related psychopathologies such as depression, PTSD and even PPD (Musazzi et al., 2018). Recently, a meta-analytic review has

found the benefits of preventing PPD, including reducing human and economic costs associated with mental illness (Sockol et al., 2013). We, and others, have shown that antenatal depression is an important risk factor for PPD (Zhao et al., 2018). In addition, PPD is also associated with an increase in the activity of the kynurenine pathway, resulting in an increase in quinolinic acid, an endogenous NMDA agonist (Wang et al., 2017). Therefore, ketamine may be used in the prophylactic treatment of PPD.

Ketamine is commonly used as a general anaesthetic in patients undergoing a caesarean section, since it can reduce postoperative pain and thereby decrease opioid need, and relieve other caesarean-associated symptoms (Lema et al., 2017). Ketamine is regarded to be safe and effective in the management of caesarean section. However, it remains to determine whether ketamine produces a prophylactic effect against PPD. In this double-blind, randomized controlled trial, we found that ketamine exerted a prophylactic effect against PPD.

2. Methods

2.1. Patients

The study was approved by the local Ethics Committee of the Central South University, Changsha, (No. P2014/s155, February 20, 2014), and was registered in the Chinese Clinical Trials Registry, (ChiCTR-ROC-17,012,944). All individuals gave their written informed consent before inclusion in the study.

The study was conducted in the Third Xiangya Hospital of Central South University, Changsha, and recruited a total 702 pregnant women, who underwent cesarean section with spinal anesthesia between August 2014 and December 2016. And they were all agreed to postoperative intravenous analgesia. Inclusion criteria were as follows (Hewitt et al., 2009): pregnant women with an American Society of Anesthesiologists

(ASA) grade II classification; age of at least 18 years old; and good communication with the man who follow-up. Exclusion criteria included unstable psychiatric disorders, electrocardiogram abnormality, hypertension and severe heart diseases, history of ketamine abuse or dependence, drug or alcohol dependence for more than 6 months, prior ineffective trial of or adverse reaction to ketamine, refusal of written informed consent, and inadequate understanding of Chinese. Finally, a total of 654 patients were included in the study, (Fig. 1).

2.2. Trial design

Demographic and basic information were collected for all participants, including: age, body mass index (BMI), employment and partner employment condition, education, and artificial impregnation or natural pregnancy. The patient's the subjective feeling was also collected regarding marriage bonds and domestic violence during pregnancy, by the reporting of one or more threats of physical, sexual or psychological/emotional violence, by any family members. A Pregnancy Pressure Scale, which contains 30 items, provided the stress-related information (Z and Huang, 1991) and were categorized into three degrees (severe, moderate or mild) during the perinatal period. In addition, trained investigators assessed antenatal depressive symptoms by EPDS (Edinburgh Postnatal Depression Scale) between gestational weeks 36–40.

Participants were randomly assigned to two groups using a random number sequence method: the ketamine group and the control group. All patients were given 0.9% saline before the operation, and were monitored for vital signs. After skin cleansing, the subarachnoid space was entered from the L3-4 or L2-3 interspace, using a 25-gauge needle. After the cerebral spinal fluid (CSF) flowed, 1.5 ml of 1% ropivacaine + 0.5 ml fentanyl + 0.5 ml 10% glucose was administered into the subarachnoid space at a rate of 0.1 ml/s. If necessary, the patient was changed to the left by 30°, and ephedrine (6–12 mg.iv) and collidate solutions were given to stabilize blood pressure. Anesthesia was controlled below the level of T6. At 10 min after delivery, ketamine (0.5 mg/kg, diluted to 10 mL with 0.9% saline) was administered in patients in the ketamine group, but not in the control group. Vital signs and adverse reactions during operation were recorded by a well trained investigator. After operation, for the patients in the ketamine group, sufentanil (100 µg), ketamine (160 mg) and palonosetron hydrochloride (0.25 mg) in 100 ml saline were given using a patient-controlled intravenous analgesia device (PCIA) device (infusion rate: 2 mL/h; bolus dose: 2 mL and lockout time: 8 min). For the patients in the control group, sufentanil (100 µg), and palonosetron hydrochloride (0.25 mg) in 100 ml saline were also given using a PCIA device (infusion rate: 2 mL/h; bolus dose: 2 mL; lockout time: 8 min). At 6 h after the operation, all patients were allowed oral liquid intake, particularly water, and within the first 24 h, some patients were allowed to have aqueous food intake. The patient was followed up by another trained investigator blinded to the experimental procedure at the hospital at 1 and 2 days postpartum and at 4–6 days postpartum and 6–8 weeks postpartum by telephone. Only the anesthesiologists, who were responsible for ketamine injection and the PCIA device, knew the group assignment, and the participants and other trained investigators were blinded to group allocation.

2.3. Measurements and outcomes

This study had two primary outcome measures, including 1) the prevalence of PPD according to the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987; Lee et al., 1998) at 6–8 weeks postpartum, and 2) the prevalence of postpartum blues at 4–6 days postpartum, which is defined as a mild and short-lasting ailment, and if postpartum blues lasts longer than 2 weeks then it is classified as neurotic depression which may need psychosocial treatment or drug therapy (Hansotte et al., 2017; Robinson and Stewart, 1986). The EPDS

has 10 items, and each item is scored on a 4-point scale (scored 0–3). A total of EPDS score of 0–30 points were calculated. The last question Item of the EPDS assesses suicidal ideation (Zhong et al., 2015). An EPDS score > 9 (Lee et al., 1998) is defined for antenatal depressive symptom and postpartum mood disorders. A logistic analysis model was used to screen the risk and protective factors related to postpartum disorders.

The secondary outcome was to examine the trial safety, including the perioperative condition (operation time, the change of heart rate, oxygen saturation and mean artificial pressure during operation); intraoperative adverse effects; and postoperative pain levels, evaluated by the 11-point Numerical Rating Scale (NRS) (Hjermstad et al., 2011).

2.4. Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences, version 22 (SPSS). Continuous variables are presented as mean ± standard deviation or as median (min and max range). A *t*-test was used to compare the different between two groups. Categorical variables are presented as frequencies and percentages, and were evaluated by χ^2 test. Data with skewed distribution was evaluated using Mann-Whitney U test. The χ^2 tests and *t* tests were used to assess the primary and secondary outcomes between the two groups. Logistic regression analysis was utilized to perform the multivariate association analysis, and were used to identify the factors related to postpartum disorders (such as age, BMI, etc.). Analysis of covariance with repeated measurements was also used to compare the data of vital signs between two groups. Probability values less than 0.05 (two tailed) were considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 654 patients completed all follow-up visits. Clinical characteristics of the two groups are shown in Table 1. There were no significant differences in the age, BMI, employment, partner employment, artificial impregnation or not, violence, primipara (Woman who has been delivered of a child for the first time), planned pregnancy, antenatal depressive symptom, education, pressure during pregnancy, and marriage bonds between the two groups (Table 1).

3.2. Primary outcomes

The PPD prevalence in the ketamine group was 12.8%, which was significantly lower than that (19.6%) in the control group ($p = 0.020$). The EPDS score at postpartum day 4 was significantly lower in the ketamine group compared with the control group ($p = 0.007$), and the prevalence of postpartum blues (11.9%) was significantly lower in the ketamine group than in the control group (18.3%, $p = 0.022$) (Table 2). Antenatal and postpartum suicidal ideation levels were not significant different between the two groups, although the reduction of suicidal ideation was significantly higher in the ketamine group compared with the control group ($p = 0.017$) (Table 3). Logistic analysis showed that the administration of ketamine was a protective factor against PPD, and stress during pregnancy, antenatal depressive symptom and antenatal suicidal ideation were risk factors for PPD (Table 4).

In the antenatal depressive maternal subgroups, the prevalence of postpartum depression in the control and ketamine groups was 35.3% and 23.8% ($p = 0.05$), respectively. For patients with antenatal suicidal ideation, the prevalence of postpartum depression in the ketamine group was 31.3% ($p = 0.02$), which was significantly less compared with the control group (62.5%). For patients who reported moderate stress, the ketamine group showed a significantly lower prevalence of postpartum depression (18.5% VS 28.6%, $p = 0.003$), compared with the control group (Fig. 2).

Table 1
Clinical characteristics of the two groups.

Characteristic		Control group	Ketamine group	P
Age	< = 35	267(81.8)	261(79.8)	0.552
	> 35	60(18.3)	66(20.2)	
BMI		29.4 ± 26.6	27.5 ± 3.1	0.193
Employment	Yes	253 (77.4)	263 (80.4)	0.338
	No	74(22.6)	64(19.6)	
Partner employment	Yes	315 (96.3)	322 (98.5)	0.085
	No	12(3.7)	5(1.5)	
Artificial impregnation	Yes	15 (4.6)	16 (4.9)	0.854
	No	312(95.4)	311(95.1)	
Domestic Violence	Yes	10 (3.1)	6 (1.8)	0.311
	No	317(96.9)	321(98.2)	
Primipara	Yes	124 (37.9)	114 (34.9)	0.416
	No	203(62.1)	213(65.1)	
Planned pregnancy	Yes	207 (63.3)	225 (68.8)	0.137
	No	120(36.7)	102(31.2)	
Antenatal depressive symptom	Yes	116(35.5)	122(37.3)	0.637
	No	211(64.5)	205(62.7)	
Education	Master degree or above	24(7.3)	34(10.4)	0.169
	bachelor's or under	303(92.7)	293(89.6)	
	Severe	24 (7.3)	20 (6.1)	
Pressure during pregnancy	Moderate	119 (36.4)	133 (40.7)	0.564
	Mild	184 (56.3)	174 (53.2)	
Marriage Bonds	Good	289 (88.4)	282 (86.2)	0.433
	Moderate	34 (10.4)	43 (13.1)	
	Bad	4 (1.2)	2 (0.6%)	

Mean ± SD or number of patients(%);p < 0.05*.

Table 2
The prevalence of postpartum blues and postpartum depression between two groups.

	Control group	Ketamine groupAVB	P
Number	327	327	
4 days postpartum			
EPDS score	5.17 ± 4.6	4.27 ± 3.8	0.007*
Prevalence of postpartum blues	60 (18.3)	39 (11.9)	0.022*
42 days postpartum			
EPDS score	5.55 ± 5.0	4.90 ± 4.3	0.074
Prevalence of postpartum depression*	64 (19.6)	42 (12.8)	0.020*

Mean ± SD or number of patients(%).

* p < 0.05.

Table 3
The suicidal ideation between two groups.

Suicidal ideation		Control group	Ketamine group	P
Antenatal period	Never	301	295	0.227
	Hardly ever	19	26	
	Sometimes	5	5	
	Often	0	1	
Postpartum period	Never	288	308	0.286
	Hardly ever	19	13	
	Sometimes	6	5	
	Often	0	1	
The change between antenatal and postpartum period.	Same	287	290	0.017*
	Worsen	16	12	
	Remission	10	25	

* p < 0.05.

3.3. Secondary outcomes

The mean operation time of the ketamine group and control group were 44.23 min and 45.33 min, respectively (p = 0.417). The analysis of covariance with repeated measurements showed that there were no statistically significant differences in the change in heart rate (F = 0.143;P = 0.705), mean blood pressure (F = 2.946;P = 0.087) and oxygen saturation (F = 0.099;P = 0.754) during operation between the two groups. The mean Numerical Rating Scale (NRS) score in the first and second postoperative day were 1.85 and 1.20 in the ketamine group, respectively which was comparable to that in the control group (1.77 (p = 0.201) and 1.22 (p = 0.673))

Adverse events occurred in the ketamine groups during the operation, including vomiting in 62 (19%) patients, dizziness in 18 (5.5%) patients, hallucination in 4 (1.2%) patients, and nystagmus in 11 (3.4%) patients. The hallucination symptoms in three patients were temporary and recovered immediately, whereas one patient who received propofol to relieve the hallucination symptom. No other psychotic symptoms such as paranoia, amnesia or thought disorders occurred in the ketamine group during the operation. Adverse events in the control group included vomiting in 30 (9.8%) cases and dizziness in 14 (4.2%) cases. The occurrence of vomiting (p = 0.01) and dizziness, (p = 0.013) were significantly less in the control group compared with the ketamine group. No other adverse reactions were observed in the control group. During PCIA time, no obvious adverse reactions were found in both groups.

4. Discussion

The present study investigated the prophylactic antidepressant effect of ketamine in patients undergoing a caesarean section. Ketamine administration resulted in a significant improvement in postpartum psychiatric disorders, as evaluated by the EPDS. Furthermore, ketamine exerted an antidepressive effect in patients with moderate stress levels during pregnancy, and in those with antenatal depressive symptom and antenatal suicidal ideation.

The NMDA receptor antagonist, ketamine, has been shown to produce rapid antidepressive effect in both preclinical and clinical studies (Fond et al., 2014; Lang et al., 2018; Oates, 2003). In the present study, we found that a sub-anesthetic dose of ketamine (0.5 mg/kg) significantly reduced depressive symptom in PPD (Iadarola et al., 2015; Murrough et al., 2013), whereas which a single low-dose ketamine (0.25 mg/kg) has been reported to exert no obvious antidepressive effect in postpartum women (Xu et al., 2017). Notably, ketamine not only decreased the prevalence of PPD, but also the prevalence of postpartum blues. Thus, our findings support the idea that ketamine can prevent postpartum psychiatric disorders.

Similar to previous studies, the present study found that stress during pregnancy was closely associated with PPD (Amat et al., 2016; Li et al., 2011). In this study, we found that ketamine produced more powerful effect in women, who reported moderate levels of stress during pregnancy, and was associated with a significantly lower prevalence of PPD. However, the beneficial effect of ketamine was not observed in women who reported mild and severe stress levels, which was similar to the study by Mion et al. Their study showed the poor prophylactic efficacy of ketamine in PTSD, which is also a stress-related disease (Mion et al., 2017). Further studies are warranted to investigate the association of prophylactic effect of ketamine with reported stress-related disease.

Our study supports a previous work showing that antenatal depression is a risk factor for PPD, and approximately 39% of patients experiencing antenatal depression develop PPD (Underwood et al., 2016). These findings highlight the overlapping pathogenesis of PPD and antenatal depression. Ketamine is well known to produce strong and rapid antidepressive effect in depressive disorders. Most studies suggest that the antidepressive effect of a single ketamine infusion only

Table 4
Logistic analysis model of the related factor and the prevalence of postpartum depression.

Postpartum depression	B	S.E	Wals	sig	EXP(B)	95% EXP(B) CI Lower limit	Up limit
Ketmine	-0.621	0.231	7.237	.007*	0.537	0.342	0.845
Pressure	-0.401	0.182	4.851	.028*	0.670	0.469	0.957
Antenatal depression	1.191	0.262	20.622	.000*	3.289	1.967	5.498
Antenatal suicidal ideation	1.025	0.320	10.260	.001*	2.788	1.489	5.222

* $p < 0.05$.

lasts for one or two weeks, thus we found that ketamine lowered the incidence of postpartum blues in the first week of the postpartum period. And it was associated with a longer-term decrease in mood in PPD woman. These results suggest that ketamine may reduce depressive symptom in the early postpartum period, thus reducing PPD risk.

In the present study, we also found that ketamine can relieve the suicidal ideation. And a positive depression screen of suicidal attempt or ideation can predict actual suicidal action, which is the leading causes of perinatal maternal mortality (Oates, 2003). In this study, suicidal ideation was screened by the last item of EPDS, which has high sensitivity but low specificity. Given the potential danger of suicidal ideation, false positive screening is more tolerable (Kim et al., 2015), in

order to maximize sensitivity. It is also of note that women with, antenatal suicidal ideation had a significantly lower incidence of postpartum blues and PPD following ketamine administration.

In the present study, we showed that a low-dose ketamine had no effect on postpartum NRS during the caesarean section, consistent with a previous study by Bilgen et al. (2012). though some reported that addition of ketamine to the PCIA improved the efficacy of postoperative anesthesia and reduced the levels of opioid consumption during caesarean section (Haliloglu et al., 2015; Heesen et al., 2015). The rapid antidepressive effect of ketamine is associated with a decrease in the levels of pro-inflammatory cytokines in the hippocampus in rodents (Wang et al., 2015). In addition, ketamine may decrease the levels of

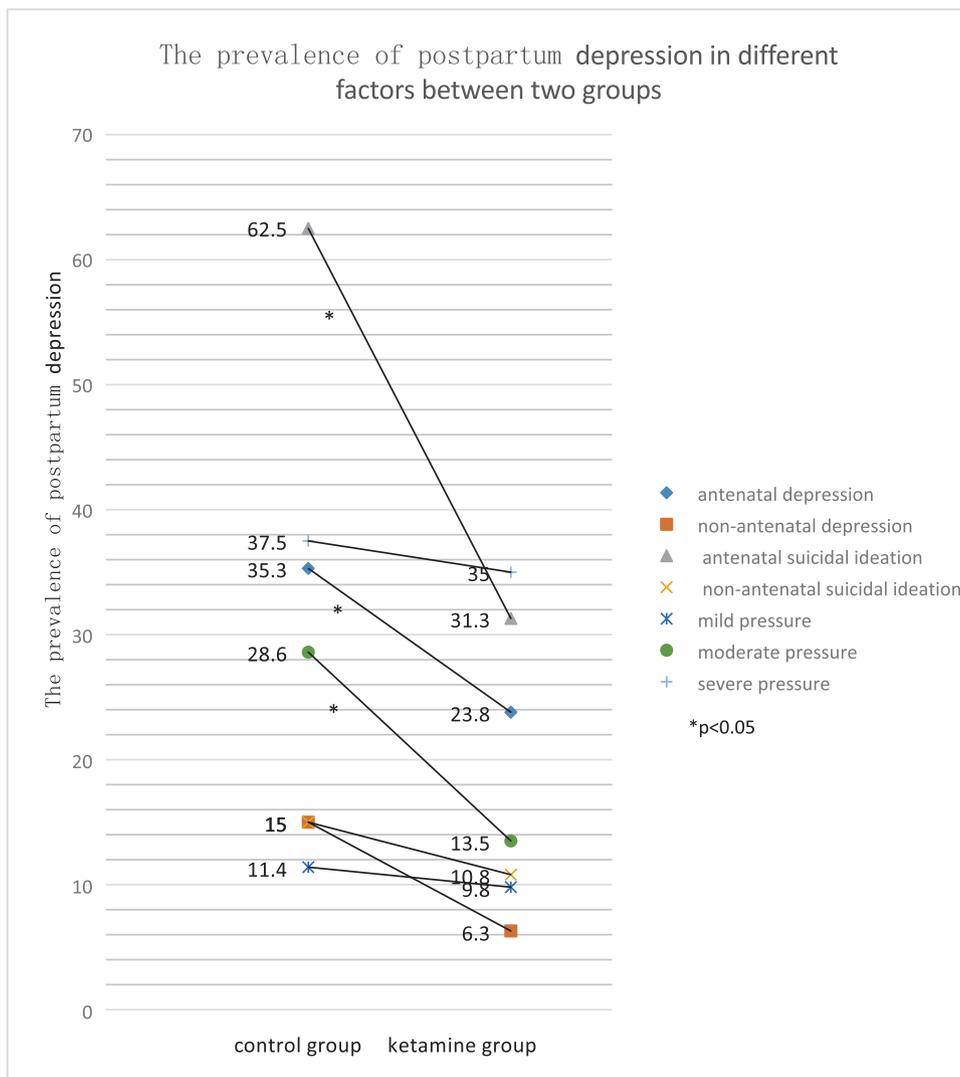


Fig. 2. The prevalence of postpartum depression in the maternal with different factors between two groups.(antenatal depression or not: $X = 3.837, p = 0.05$; $X = 2.73, p = 0.098$, antenatal suicidal ideation or not: $X = 5.419, P = 0.020$; $X = 3.743, p = 0.053$, different pressure during pregnancy: $X = 0.254, p = 0.614$; $X = 8.672, p = 0.003$; $X = 0.029, p = 0.864$).

indoleamine 2,3-dioxygenase (IDO) induced by pro-inflammatory cytokines in rodents (Zhang et al., 2016), thereby lowering the products of the kynurenine pathway that are associated with depression (Moaddel et al., 2018). Furthermore, we have recently found that the IDO alleles are associated with the level of PPD symptomatology (Duan et al., 2018). Ketamine can increase the levels of serotonin and melatonin, which contribute to the mother's well-being and antioxidant status (Anderson and Maes, 2013). Taken together, these findings suggest that the increased PPD risk of antenatal depression, moderate stress and suicidal ideation may be mediated by changes in the interactions of inflammatory processes, IDO and the kynurenine pathway.

In summary, we found that the prophylactic administration of ketamine during the perioperative period was beneficial to the postpartum mood. Ketamine administration was relatively safe, since it produced only some transient adverse effects and no obvious adverse effect was observed during the use of PCIA. It has been reported that ketamine administration by epidural bolus does not induce any significant side-effects in women undergoing a caesarean section (Heesen et al., 2015). Future studies are warranted to determine whether the side effects of ketamine can be prevented by other administration route. In addition, it is necessary to explore the precise antidepressive mechanism of ketamine in women in the future.

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6. Conflict of interest

There are no personal, organizational or financial conflicts of interest.

Authors' contribution

Sai-Ying Wang designed the trial. Shi-Chao Luo and Li-Fei Wan was responsible for the group allocation and anesthesia. Jia-Hui Ma, Dan-Yang Li and Shan-Shan Zheng followed up the patients. He-Ya Yu analyzed data. Jia-Hui Ma wrote the first draft of the manuscript. Sai-Ying Wang and Kai-Ming Duan revised the manuscript. All authors contributed to and have approved the final manuscript.

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