Original Article

Acute Administration of Zn, Mg, and Thiamine Improves Postpartum Depression Conditions in Mice

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Abstract

Background: Postpartum depression (PPD) affects approximately half of new mothers. Chronic exposure to progesterone during pregnancy and its withdrawal following delivery increases depression and anxiety. In addition, there are complex interactions between hormones, neurotransmitters, and trace elements. Zinc (Zn) and magnesium (Mg) influence the nervous system by impacting synaptic neurotransmission in the brain. Thiamine (Vit B_1) deficiency results in a high percentage of depressive behaviors. Elevated levels of reactive oxygen species in pregnancy are implicated in the pathogenesis of major depression.

Methods: We examined the effects of different combinations of Zn, Mg, and Vit B_1 in an animal model of PPD. ZnCl, MgCl, and thiamine-HCl were administered to PPD-induced mice. Depression, anxiety-related behavior, and total antioxidant capacity (TAC) were assessed. Depression and anxiety-like behavior were evaluated by the forced swimming test (FST) and elevated plus-maze, respectively.

Results: The acute combined administration of Zn, Mg, and Vit B_1 significantly decreased immobility time in FST, increased the percentage of both time spent in- and entries to open arms in the elevated plus-maze, and augmented TAC.

Conclusion: Our data suggest that acute administration of combined treatment with Zn, Mg, and Vit B_1 on postpartum day 3 improves depressive symptoms and anxiety-like behaviors. Our evaluation of TAC is in accordance with behavioral results.

Keywords: Anxiety, depression, magnesium, thiamine, Zinc

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Introduction

A depressed mood is common during the postpartum period, affecting almost 50% of new mothers during the first days following delivery. This transient mood disturbance in vulnerable women may lead to more serious and persistent depression during subsequent weeks, finally fulfilling the diagnostic criteria for major depression, known as postpartum depression (PPD).[1,2] Evidence suggests that maternal depression is harmful for new mothers, their infants, and family relationships. PPD can also impair the infant's cognitive and social development. This situation can even lead to suicidal tendencies or infanticide.[3–5]

Rapid decline in hormone levels, in particular sex hormones, happens following delivery. Based on previous studies, withdrawal of progesterone has been proposed as a trigger for PPD symptoms and recent attention has been given to the possible mood effects of neuroactive metabolites and precursors of progesterone. Because depression is often accompanied by enhanced anxiety, chronic exposure to progesterone, followed by its withdrawal increases anxiety.[6–10] It is possible that complex interactions between hormones and neurotransmitters are involved; because of this, alterations in ovarian steroids are associated with debilitating psychiatric and neurological disorders that include premenstrual dysphoric disorder, premenstrual syndrome, menstrual migraine, PPD, and anxiety. Based on recent studies, trace elements such as zinc (Zn) and magnesium (Mg) also exert their antidepressant effects by acting on neurotransmitter pathways.[11–14]

Zn is a trace element, particularly abundant in the central nervous system (CNS). Zn is important as a signaling factor in synaptic neurotransmission in the brain.[15,16] Several studies have shown its potential antidepressant activity in humans and suggest that Zn may be involved in the mechanism of action of antidepressant therapy. In confirmation, anxiety-like behavior is increased in Zn-deprived rodents.[17–19] In another study, the results have demonstrated a relationship between the severity of depressive symptoms and decreased serum Zn concentrations in humans with PPD.[20]

Mg is a trace element that acts primarily as an intracellular ion influencing the nervous system by its effects on the release and metabolism of neurotransmitters.[21,22] Mg has been proposed to participate in biochemical dysregulation that contributes to psychiatric disorders. The results of several studies indicate that Mg induces antidepressant and anxiolytic-like effects in mice without development of tolerance to these actions, which is suggestive of its potential antidepressant and anxiolytic activity.[9,23] The fetus and placenta absorb huge amounts of nutrients, particularly Mg, from the mother and loss of Mg is hypothesized to be a contributing factor in the development of PPD.[24]

Thiamine (Vit B_1) deficiency also can occur in eating disorders and hyperemesis gravidarium. This condition shows a high percentage of aggressiveness, confusion, memory impairments, and depressive behaviors in animal models of Vit B_1 deficiency where antidepressants such as imipramine can suppress this depressive

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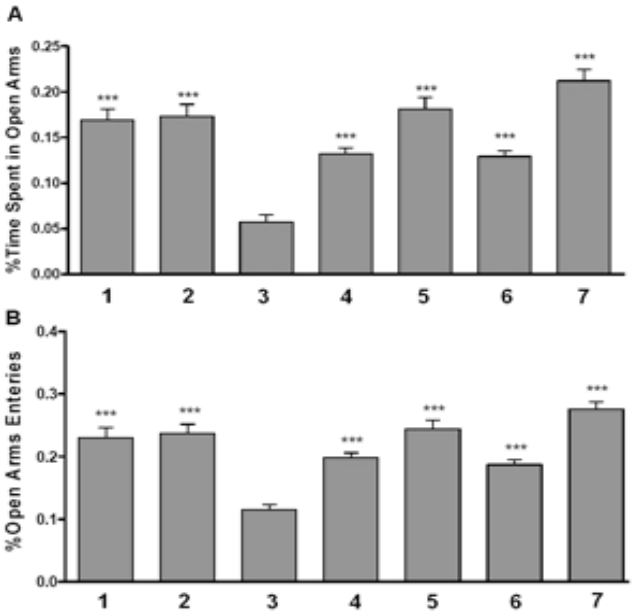

Figure 1. Percentage of time spent in open arms (A) and number of entries (%) into open arms (B) of the elevated plus-maze (EPM) measured during 5 minutes. 1: Saline, 2: Sesame oil, 3: PWD, 4: Zn+Mg, 5: Zn+Vit B_1, 6: Mg+Vit B_1, and 7: Zn+Mg+Vit B_1. Treatment doses are as follows: saline (2 ml/kg); sesame oil (2 ml/kg); progesterone (5 mg/kg); Zn: (30 mg/kg); Mg (30 mg/kg); Vit B_1 (50 mg/kg). Columns represent the mean±SEM (n=10 per group). *P*<0.001 compared to the PWD group: It is common in original articles about figures of EPM and FST.

behavior.[25,26]

Oxidative stress is the imbalance between oxidative and antioxidative systems in favor of the former and has been implicated in the pathophysiology of several neuropsychiatric diseases, including major depressive disorder. A measurement of total antioxidant capacity (TAC) can provide information about overall antioxidant status which may include those antioxidants not yet recognized or not easily measured.[27,28]

Despite the high prevalence of PPD, up to half of the cases of postpartum disorders remain undiagnosed or untreated.[29] Although women with PPD may seek psychotherapy as an initial treatment, it is not always effective. Those with severe symptoms may need antidepressant therapy, but the high cost and side effects of antidepressant drugs remain important treatment obstacles for many.[30,31] Many women choose nonpharmacological interventions, due to the potential transmission of drugs into breast milk and fear of addiction or drug dependence.[32] As mentioned above, a single administration of Zn and Mg improves depression and anxiety-related behavior. In addition, based on the literature and our pilot study, Vit B_1 has been shown to have antidepressant and anxiolytic effects. Therefore, the aim of the present study was to evaluate the therapeutic effects of different combinations of Zn, Mg, and Vit B_1 on an animal model of PPD. We assessed depressant-like and anxiety-like behaviors, as well as TAC.

Materials and Methods

Experimental animals

Female albino NMRI inbred mice, weighing 25 – 30 g and 6 – 8 weeks old were used. Animals were housed in groups of 4 – 5 with free access to food and water. Animals received food pellets that contained 18.7% protein, 3% fat, 0.65% calcium, 0.68% phosphorus, and 2600 Kcal/Kg with supplementary vitamins and minerals adequate for daily requirements. All behavioral experiments were conducted during 12:00 and 18:00. Mice were housed in a temperature controlled room (21 ± 1°C). Throughout each experiment, mice were maintained on a 12 hour light, 12 hour dark cycle. All procedures were carried out in accordance with the Guidelines for Animal Care and Use at Tehran University of Medical Sciences. All mice were allowed to adapt to their caging environment for at least one week prior to the induction of PPD.

Experimental design

PPD was conducted according to the protocol by Beckley and Finn.[6] For this purpose, 50 animals were divided equally into 5 groups (n = 10) of progesterone withdrawal (PWD) and treatment (Zn + Mg, Zn + Vit B_1, Mg + Vit B_1 and Zn + Mg + Vit B_1). All animals received daily injections of progesterone for 5 days after which progesterone was withdrawn for 3 days.

In a preliminary study to confirm the effect of PWD, 2 groups, which received saline and sesame oil instead of progesterone served as the control groups. Various combinations of $ZnCl_2$, $MgCl_2$ and thiamine-HCl in the corresponding groups were administered on the 8th day at 30 minutes before the open field, elevated plus-maze (EPM) and forced swimming tests (FST) in the treatment groups.[12,33,34] After the last test, mice were decapitated under deep anesthesia and approximately 1 ml of blood was quickly collected. After centrifugation for 3 minutes at 3000 rpm, serum was collected in a test tube and stored at -70°C for measurement of TAC.

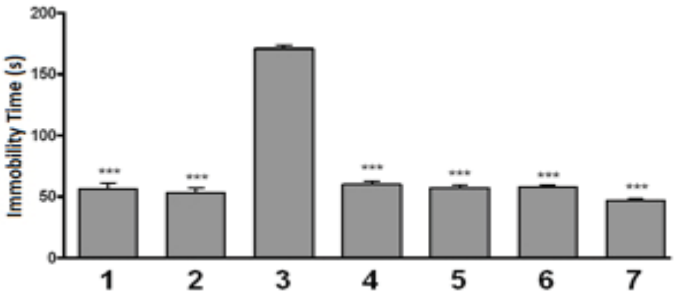

Figure 2. Immobility time in the forced swim test (FST) of 7 groups of mice. Immobility time was measured over 4 minutes. 1: Saline, 2: Sesame oil, 3: PWD, 4: Zn+Mg, 5: Zn+Vit B1, 6: Mg+Vit B1, and 7: Zn+Mg+Vit B1. Treatment doses are as follows: saline (2 ml/kg), sesame oil (2 ml/kg), progesterone (5 mg/kg), Zn (30 mg/kg), Mg (30 mg/kg), and Vit B1 (50 mg/kg). Columns represent the mean±SEM (n=10 per group). P<0.001 compared to PWD group.

Drugs and treatments

Progesterone, $ZnCl_2$, $MgCl_2$, and thiamine-HCl (Sigma, St. Louis, MO, USA) were used in the study. Progesterone was dissolved in sesame oil (2.5 mg/ml) and injected intraperitoneally (5 mg/kg). ZnCl (30 mg/kg), $MgCl_2$ (30 mg/kg), and thiamine-HCl (50 mg/kg) were dissolved in saline. All solutions were prepared immediately before the experiments and all injections were administered intraperitoneally with the exception of thiamine-HCl which was administered subcutaneously. Drugs were administered in a volume of 2 ml/kg.

Open field locomotor activity

First, we assessed the ambulatory behavior of mice in an open field test to ensure that alterations in the duration of immobility did not result from the changes that occurred in motor activity. The apparatus consisted of a wooden box that measured 40 × 60 × 50 cm. The floor of the arena was divided into 12 equal squares. The animals were gently placed in the center of the field and the number of squares crossed with all paws (crossing) was counted in a 6-min session.[35]

Elevated plus-maze test (EPM)

The plus-maze apparatus was made of Plexiglas and consisted of 2 open (30 × 5 cm) and 2 enclosed (30 × 5 × 15 cm) arms. The arms extended from a central platform of 5 × 5 cm. The apparatus was mounted on a Plexiglas base which was raised 38.5 cm above the floor and illuminated by a red light. For the test, we placed a mouse in the center of the apparatus (facing an enclosed arm) and allowed it to explore freely. The number of entries into the open arms and the time spent in these arms were scored for a 5-minute test period. An entry was defined as the placement of all 4 paws within the boundaries of the arm. The following measures were calculated from the test: percentage of entries into the open arms, and time spent in the open arms, expressed as a percentage of the time spent in both the open and enclosed arms. Anxiolytic activity was determined by increases in time spent in the open arms or in the number of open arm entries.[36,37]

Forced swimming test (FST)

Mice were individually placed in an open cylindrical container (diameter 10 cm, height 25 cm), filled to 19 cm with water at a temperature of 23 ± 1°C. Mice were allowed to swim for 6 minutes. Behavior was analyzed by 2 experienced raters blinded to the drug treatments. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above the water. The duration of immobility was recorded during the last 4 minutes of the test.[38,39]

Evaluation of total antioxidant capacity (TAC)

The assay is based on the incubation of [2, 20-azino-di-(3-ethylbenzthiazoline-6- sulphonic acid) (ABTS)] with peroxidase (metmyoglobin) and H_2O_2 to produce the radical cation ABTS•+ which has a relatively stable blue-green color, the absorbance of which can be measured at 734 nm. When the colored ABTS•+ is combined with an antioxidant substance, it is reduced to its original colorless ABTS form. Antioxidants in the added sample cause suppression of this color production to the degree that is proportional to their concentration. Bovine serum albumin, the Trolox equivalent antioxidant activity, was used as a standard.[40,41]

Statistical analysis

Data were expressed as mean ± SEM and comparisons between treatment and PWD groups were performed by one-way ANOVA. When appropriate, post-hoc analyses were performed using the Tukey's test following ANOVA. A value of $P < 0.05$ was considered significant.

Results

Spontaneous locomotor activity

In all of the treatment groups, the number of squares entered was not more than the PWD group (data not shown).

Elevated plus-maze (EPM)

The inter-rater reliability coefficient for the 2 observers that scored the EPM behavior was 0.87 for the open arm time ($P < 0.05$). Figure 1A shows the percentage of time spent in the open arms among the experimental groups. ANOVA followed by Tukey's test showed significant differences in the experimental groups with regards to the percentage of time spent in the open arms. The saline and sesame oil groups spent significantly more time in the open arms than the PWD group ($P < 0.05$). All treatment groups had statistically significant increases in the time spent in the open arms compared to the PWD group ($P < 0.05$). The highest percentage of the time spent in the open arms was noted for the Zn + Mg + Vit

Table 1. Plasma total antioxidant capacity (TAC) levels

Groups	TAC (nmol/mg protein)
Saline[a]	208 ± 0.032
Sesame oil[a]	207 ± 0.021
Progesterone[b]	169 ± 0.054
Zn+Mg[c]	195 ± 0.052
Zn+Vit B_1[d]	184 ± 0.047
Mg+Vit B_1[d]	181 ± 0.043
Zn+Mg+Vit B_1[a]	206 ± 0.071

Data are expressed as mean±SEM (n=10 per group). a-d: Different letters have statistically significant differences (P<0.05). TAC: Total antioxidant capacity.

B_1 group, whereas the least was seen in the PWD group. (F6, 69 = 22.72, P < 0.05). Figure 1B shows the percentage of entries into the open arms by mice in each experimental group.

The saline and sesame oil groups had significantly more open arm entries when compared with the PWD group (P < 0.05). In addition, there were significant differences in the treatment groups compared with the PWD group (P < 0.05). The highest percentage of open arm entries belonged to the Zn+Mg+Vit B_1 group and the least to the PWD group (F6,69 = 19.33, P < 0.05).

Forced swimming test (FST)

The inter-rater reliability coefficient for the 2 observers who scored the behaviors in the FST was 0.86 (P < 0.05). The results depicted in Figure 2 show that the saline and sesame oil groups spent significantly less time immobile than the PWD group (P < 0.05). All treatment groups spent significantly less time in the immobile state when compared with the PWD group (P < 0.05). Combined administration of Zn + Mg + Vit B_1 caused the greatest reduction in immobility time (F 6, 69 = 193. 8, P < 0.05).

Total antioxidant capacity (TAC)

As shown in Table 1, significant differences existed in TAC levels among the saline, sesame oil, and all treatment groups compared to the PWD group. (F6, 69 = 33.73, P < 0.05).

Discussion

The aim of the present study was to determine whether acute combined administration of Zn, Mg and Vit B_1 improves depressive symptoms, as evaluated by immobility time in the FST and anxiety-like behaviors of PPD in mice. We observed a significant decrease in immobility in the FST and a significant increase in percentages in the open-arm entry and open-arm time spent in the EPM in all treatment groups. Despite the decrease in immobility time in FST, the open field test showed no augmentation in locomotor activity, which suggested that the results of the FST were not affected by our treatments. The TAC after administration of Zn, Mg, and Vit B_1 significantly increased.

Reports of several studies have supported the hypothesis that a significant increase in depression-like behavior is detectable at least 3 days after delivery.[6,42] In the present study, we showed that at 3 days of PWD, along with acute administration of various combinations of Zn, Mg, and Vit B_1 there was antidepressant and anxiolytic-like behavior in mice as seen by the FST and EPM in the treatment groups. Our experiment showed anxiogenic-like behavior at 3 days of PWD, while Bitran and Smite have demonstrated anxiogenic-like behavior one day following PWD.[43] According to our results, the greatest reduction in immobility was in the Zn + Mg + Vit B_1 group. Our results showed the most increase in time spent in the open arms and the highest number of open arm entries was in the same group, which confirmed the synergistic effects of these components.

Previous studies have shown that Zn decreases immobility time in the FST.[17,44] Interactions of inhibitory and excitatory amino acid neurotransmitters with Zn are well known.[45] Zn supplementation can potentiate the effects of antidepressant drugs and it has been demonstrated that depression is possibly accompanied by lower serum Zn concentrations.[18,46] The antidepressant-like effects of Zn have been shown in an animal model of depression, as assessed by the tail suspension test.[47] Zn deprivation is linked to an increase in anxiety-like behavior. [19] Zn may play a role in synaptic neurotransmission in the mammalian brain and serves as an endogenous neuromodulator of several important receptors, channels, and enzymes. For example, Zn inhibits NMDA, $GABA_A$ receptors and nitric oxide synthase (NOS) which are believed to be important molecular targets for antidepressants. Zn also augments α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and ATP-sensitive potassium (K_{ATP}) channel activity.[16,44,46,48]

Based on other studies, Mg has antidepressant and anxiolytic activity; activation of the NMDA receptor ion channel is blocked by Mg in a voltage-dependent manner.[9,23] Mg is a natural calcium channel blocker necessary for relaxation and appropriate nerve function. Calcium stimulates nerves and Mg relaxes them. These systems have been reported to be involved in the pathophysiology of depression. Mg also suppresses the Ca^{++}-protein kinase C related neurotransmission and stimulates Na-K-ATPase.[45,49]

The NMDA class of glutamate receptors and NO signaling pathway are involved in the pathophysiology of major depression.[50] The presence of NOS in regions such as the hypothalamus, amygdale, and hippocampus is associated with anxiety. Acute inhibition of NO synthesis by the use of a variety of antagonists has led to anxiolytic or anxiogenic effects depending on the animal and the method of anxiety evaluation.[51] In this manner, dysfunctions in $GABA_A$ receptor regulation during pregnancy and the postpartum period may causedepression-like and anxiety-like behaviors during postpartum. However the differential actions of neurosteroids such as progesterone are dependent on anatomical connections and $GABA_A$ receptor distribution.[8,52]

In animal models, thiamine-deficient (TD) mice show increased duration of immobility in the FST swimming test. NMDA receptor antagonists provide significant neuroprotection in some of the brain areas susceptible to Vit B_1 deficiency.[26] The results of this study have indicated that the time spent in the open arms and the numbers of open arm entries in the Zn + Mg + Vit B_1 group were more than those of the Zn + Mg group. This increase might be mediated by Vit B_1.

Oxidative stress occurs as a consequence of an imbalance between the formation of oxygen-free radicals and inactivation of these species by an antioxidant defense system.[53] Oxidative stress has been found in pregnant mothers. It is well known that pregnancy is itself a state of oxidative stress arising from the increased metabolic activity in placental mitochondria and the reduced scavenging power of antioxidants.[54] Reactive oxygen species are implicated in the pathogenesis of various neuropsychiatric disorders, including major depression.[55] Major depression is associated with increased levels of serum superoxide dismutase (SOD), serum, and erythrocyte malondialdehyde (MDA), and decreased levels of plasma ascorbic acid.[56,57] Changes in antioxidative parameters can serve as a characteristic element of depression and help to assess the effects of pharmacological treatment.[58]

Antioxidant capacity can be defined as the ability of a compound to reduce pro-oxidant activity. It appears that TAC is tightly regulated in serum or plasma in neurological disorders, however, some studies have failed to demonstrate this. Sofic and colleagues did not find significant differences in total serum antioxidant capacity in patients with Parkinson's and Alzheimer's diseases, amyotrophic lateral sclerosis (ALS), depression and schizophrenia when compared to healthy control subjects.[59] In agreement with our results, Cumurcu and colleagues have reported that the serum total oxidant status (TOS) and oxidative stress index (OSI: ratio of TOS to TAC) were significantly higher along with a significantly lower TAC in the pre-treatment stage in major depressive disorder (MDD) patients compared to the healthy control group. Serum TOS and OSI significantly decreased, whereas TAC significantly increased in the post-treatment stage compared to the pre-treatment stage in MDD patients.[27]

Oxidative stress conditions can also induce excessive NO production by activating inducible NOS activity. NO reacts rapidly with reactive oxygen species (ROS) leading to protein nitration and vascular cell injury.[60]

PPD and anxiety are important concerns for the mother, infant, and family. Based on our findings, acute administration of combined Zn, Mg, and Vit B_1 3 days after delivery improved depressive symptoms and anxiety-like behavior. Our findings in the evaluation of TAC have confirmed this hypothesis. However we have investigated only TAC while more tests, such as SOD and MDA could have been performed to better analyze the changes in the antioxidant system. We suggest that oral administration of these elements along with other trace elements and vitamins should be investigated in future studies. The dosages in this study are for mice and their appropriateness for humans should be examined. Possible pharmacokinetic interactions between Zn, Mg, and Vit B_1 need to be further investigated for safety considerations.

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