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Ascorbic acid effect on morphine withdrawal symptoms in rats

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ABSTRACT

Introduction: Today, drug addiction is an important healthcare issue. Any helps to drug withdrawal may decrease its prevalence in the society. Ascorbic acid is a component, which can affect neurotransmitter systems as a regulator along with its cofactor role. Noradrenergic and dopaminergic systems are two important neurotransmitter systems in the opiate withdrawal syndrome. It seems that ascorbic acid can decrease the symptoms of opiate withdrawal through regulating the related systems. In this regard, the current study aimed to evaluate the effect of ascorbic acid on the symptoms of morphine withdrawal in Syrian mice.

Materials and Methods: Male Syrian mice in eight experimental groups received incremental doses of morphine as 10, 20, 30 and 40mg/kg within the first, second, third, and fourth days of the experiment, respectively, through intraperitoneal injection, twice a day, and the control group received and equal amount of saline. On the fifth day, six groups of morphine addicts received ascorbic acid with six doses of 10, 50, 100, 200, 400 and 800mg/kg through intraperitoneal injection. Then, naloxone 2mg/kg was injected to all groups including morphine alone and morphine with acute does of ascorbic acid. Then, withdrawal symptoms were evaluated for 30 minutes.

Results: Administration of an acute dose of ascorbic acid reduced dose dependent withdrawal symptoms in such a way that 10, 50, and 100mg/kg doses of ascorbic acid reduced "writhing" symptom, 200mg/kg reduced "jumping" symptom, and 400 and 800mg/kg reduced "climbing, jumping, and standing" symptoms.

Conclusion: It seems that ascorbic acid administration can improve the symptoms of opiate withdrawal syndrome. More studies on human population can also indicate the therapeutic effect of ascorbic acid on drug withdrawal.

Keywords: Addiction; Morphine; Withdrawal syndrome; Ascorbic acid.

Introduction

Addiction is one of the most important social problems, which affects the personal life the addicts in different ways. Addicts may consume different drugs. One of the most common drugs among the Iranian society is opium. Some addicts try to withdraw following personal and social problems of addiction, but bother-

rsome symptoms of withdrawal period stops them [1]. Symptoms such as muscular pains, irritability, restlessness, and digestive problems are sometimes so severe in withdrawal period that frighten the patient and his/her relatives, and prevent completion of the treatment period [2]. Neurotransmitter changes in different systems such as noradrenergic, dopaminergic, and GABAergic are the main reasons for addiction and withdrawal syndrome [3]. Among the mentioned systems, GABAergic plays the main role in addiction, since narcotic drugs lead to release large amount of dopamine and cause addiction through stimulation of this system [4]. Opioids also cause addiction through stimulation of this system and by continuing drug consumption, physiological and adaptive changes such as changes in receptors, and affecting the second messengers, enzymes are produced and genes expressed. When opioid consumption is stopped the created balance is shifted and some nervous pathways are disrupted.

Opiate withdrawal syndrome is the final result of this disruption. Narita et al. showed that locus coeruleus, balancing the noradrenergic systems, is one of the regions which its activity increases during opioids withdrawal [5]. Ascorbic acid (vitamin C) is a water-soluble antioxidant which significantly accumulates in mammalian brain. Recent studies showed that this vitamin plays neurotransmitter and neuromodulator roles in biological reactions, along with its cofactor role. In some parts of the brain, ascorbic acid molecule works as a signaling molecule [6]. Alaei et al. reported that ascorbic acid is released from glutamine neurons in striatum and nucleus accumbens and regulates dopaminergic and GABAergic systems [7].

Other studies reported that following the consumption of addictive drugs, releasing ascorbic acid in brain regions increases [8]. In such a way that some researchers believe that ascorbic acid plays a regulating role in addiction process, especially addiction to narcotics [9]. Some studies on animals showed that simultaneous administration of chronic doses of ascorbic acid along with morphine reduces the tendency toward this drug and they showed less bothersome symptoms of withdrawal [10]. Other studies showed that administration of ascorbic acid during opioid withdrawal period can decrease withdrawal symptoms [11]. Since regulating bothersome symptoms of withdrawal can increase the tendency of addicts toward drug withdrawal, the current study aimed to evaluate the effects of acute doses of ascorbic acid on opioid withdrawal symptoms in Syrian mice.

Materials and Methods

The current study used mature NMARI Syrian male mice, weighting 250-300g. Rats were kept in animal house at 22±2˚C, 12/12 light-dark cycle, and free access to water and food. Rats were studied in eight experimental groups. The first group only received saline (with the same amount of morphine) and the second group only received morphine. Groups 3 to 8 received different doses of ascorbic acid from 10mg/kg to 800mg/kg in addition to morphine. To adapt animals to morphine, twice a day they received increasing doses of morphine through intraperitoneal injection as 10mg/kg, 20mg/kg, 30mg/kg, and 40mg/kg on the first, second, third, and fourth days of experiment, respectively. On the fifth day, groups 3 to 8 received 2 mg/kg naloxone through intraperitoneal injection after receiving ascorbic acid, and then the withdrawal symptoms were studied for 30 minutes; after receiving naloxone, each rat was immediately placed in a transparent Plexiglas box and the symptoms such as writhing, climbing, jumping, and standing were recorded, within 30 minutes. To statistically compare parameters between the groups under experiment, ANOVA and then Tukey test were used. To compare parameters between the experimental and control groups, when creating addiction or withdrawal symptoms, Student t-test and Mann-Whitney test were employed in case of parametric and non-parametric data respectively. $P<0.001$, $P<0.01$, $P<0.05$ were considered as level of significance based on the test.

Results

The current study evaluated the effect of receiving acute doses of ascorbic acid on opiate withdrawal symptoms and results showed that regulating morphine withdrawal symptoms can have association with ascorbic acid doses in such a way that different doses had different effects. Doses 10-50 and 100mg/kg of ascorbic acid reduced writhing symptom, but had no effect on the other symptoms; 200mg/kg of ascorbic acid reduced jumping, but had no effect on the other symptoms. Doses of 400 and 800mg/kg of ascorbic acid reduced climbing, standing and jumping symptoms, but showed no effect on writhing. Writhing only reduced with low doses of ascorbic acid and did not change with high doses. The effect of different doses of ascorbic acid on morphine withdrawal symptoms is shown in figures 1 to 4.

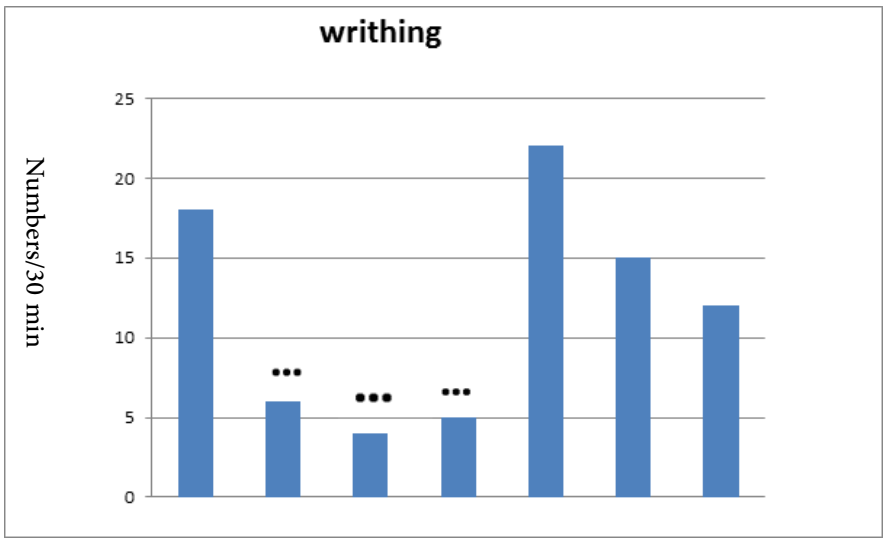

Figure 1. Effect of different doses of ascorbic acid on the writhing symptom mean during morphine withdrawal period.

● =P<0.05, ●● =P<0.01, and ●●● =P<0.001 significant difference with morphine group.

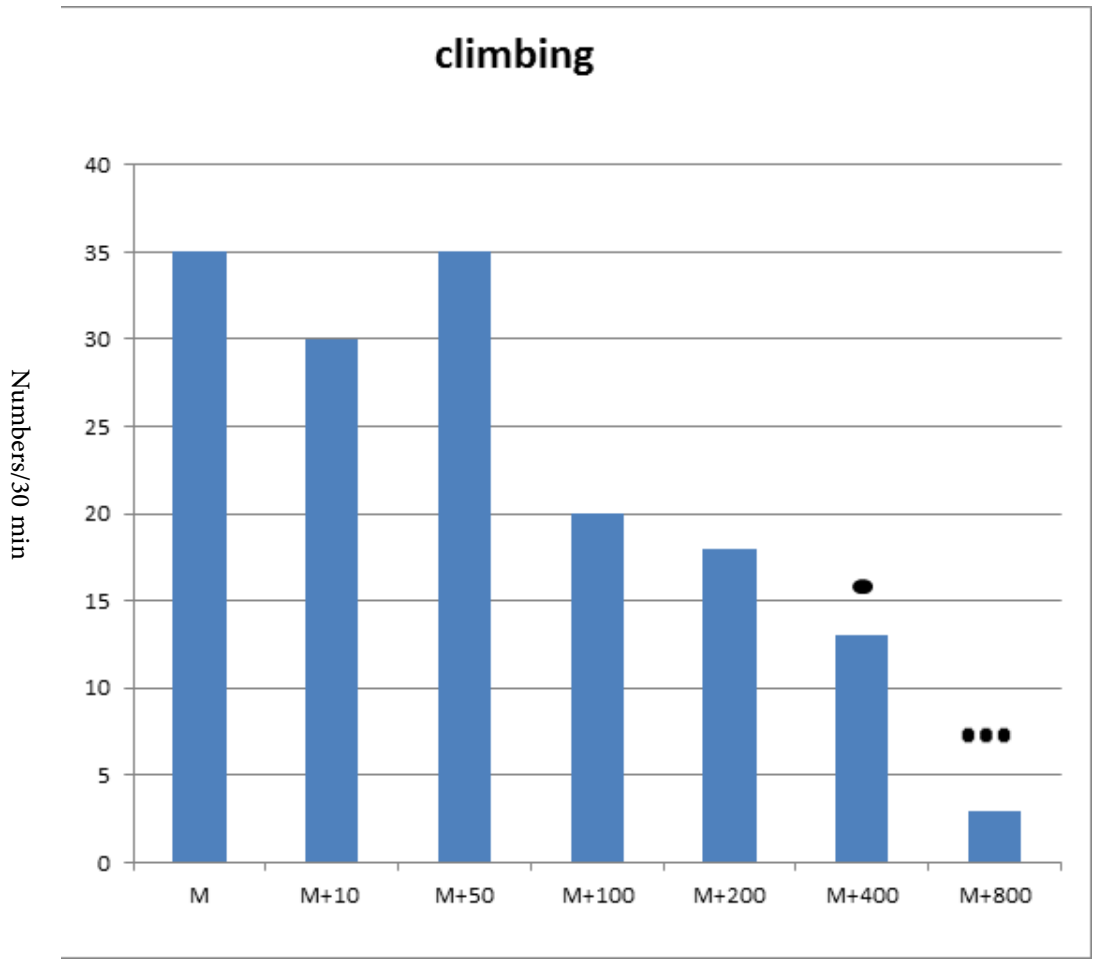

Figure 2. Effect of different doses of ascorbic acid on the climbing symptom mean during morphine withdrawal period.

● =P<0.05, ●● =P<0.01, and ●●● =P<0.001 significant difference with morphine group.

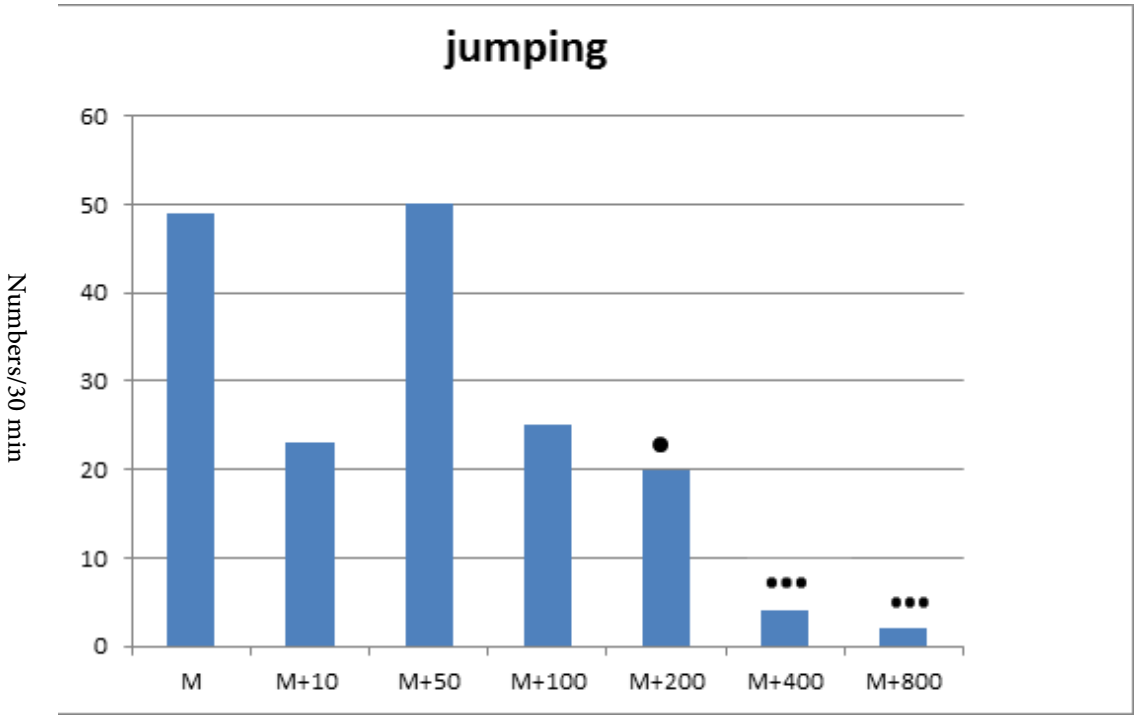

Figure 3. Effect of different doses of ascorbic acid on the jumping symptom mean during morphine withdrawal period.

● =P<0.05, ●● =P<0.01, and ●●● =P<0.001 significant difference with morphine group.

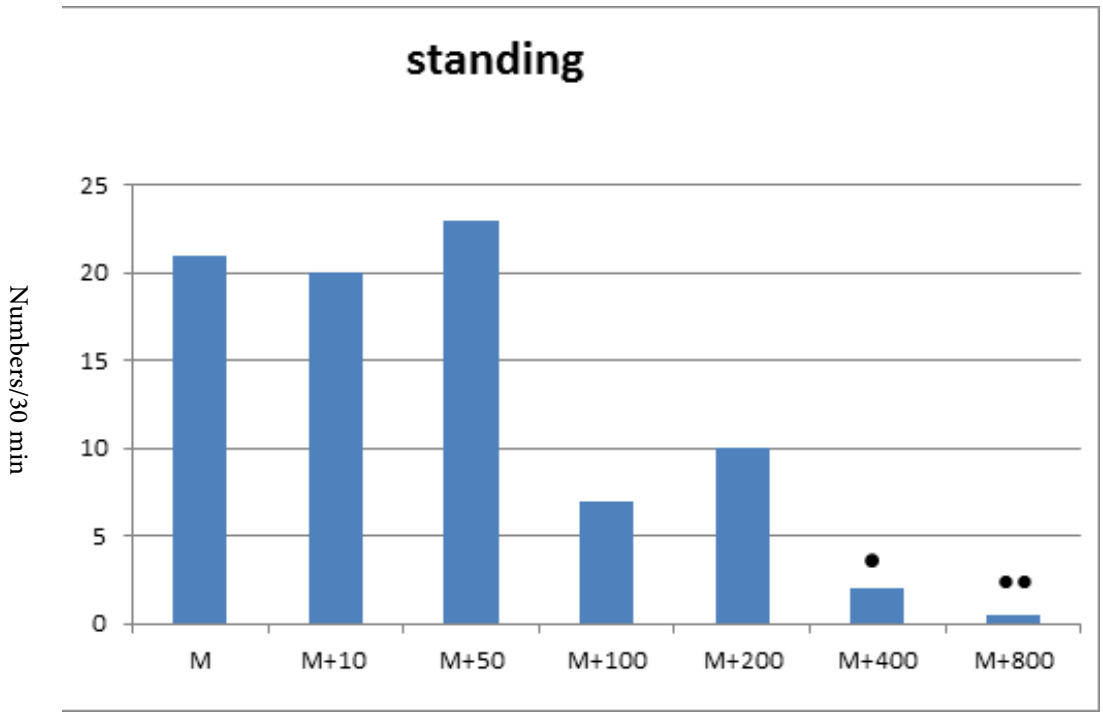

Figure 4. Effect of different doses of ascorbic acid on the standing symptom mean during morphine withdrawal period.

● =P<0.05, ●● =P<0.01, and ●●● =P<0.001 significant difference with morphine group.

Discussion

Different neurotransmitter changes are the reason for opiate withdrawal symptoms. Noradrenergic and dopaminergic systems are two important and effective neurotransmitters [12]. The current study evaluated the effect of acute doses of ascorbic acid on morphine withdrawal symptoms, during withdrawal period. Results obtained by Rafati et al. were compatible with those of the current study [13]. The present study showed that regulating some symptoms of opiate withdrawal syndrome were dependent on ascorbic acid doses; the highest effect was generally observed in high doses of ascorbic acid. Doses 10-50 and 100mg/kg of ascorbic acid reduced only writhing, and dose of 200 mg/kg of ascorbic acid reduced only jumping symptom but nothing of these doses had no effect on the other symptoms. Doses 400 and 800mg/kg of ascorbic acid reduced standing, jumping, and climbing, but had no effect on writhing. Results of the study by Evangelue et al. were compatible with those of the current study [14]. In the current study, writhing was reduced only with low doses of ascorbic acid and high doses had no effect on it. Esmaeili et al. showed that high doses of ascorbic acid can intensify writhing symptom [14,15].

The effectiveness of ascorbic acid on opioid withdrawal symptoms may associate with the role and intervention of different neurotransmitters, receptors, and multiple neural pathways in opiate withdrawal syndrome [14,16]. In the current study, ascorbic acid was used to regulate the opiate withdrawal syndrome, following the creation of this syndrome in morphine addicted rats. In some studies, simultaneous administration of morphine and ascorbic acid was used to decrease the tendency toward morphine consumption [17]. Since increasing the secretion of glutamate during opiate withdrawal syndrome leads to destruction of brain neurons, some studies stopped this destruction through administration of ascorbic acid during the syndrome secretion [18]. Some human based studies showed that high doses of ascorbic acid before receiving naloxone can reduce the severity of naloxone withdrawal symptoms [19]. Other studies showed that intravenous receiving vitamin C in patients with cancer can reduce their pains [20].

Conclusion

The reason could be that vitamin C improves endogenous opiate system. Further studies could indicate the effect of ascorbic acid on reducing morphine withdrawal symptoms and help the treatment of drug addicts.

Conflict of Interest

There is no conflict of interest to declare.

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