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Original Article

The electrical stimulation of the central nucleus of the amygdala in combination with dopamine receptor antagonist reduces the acquisition phase of morphine-induced conditioned place preference in male rat

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Abstract

Background and purpose: The central nucleus of the amygdala (CeA) is one of the nuclei involved in the reward system. The aim of the current study was to investigate the electrical stimulation (e-stim) effect of the CeA in combination with dopamine D1 receptor antagonist on morphine-induced conditioned place preference (CPP) in male rats.

Experimental approach: A 5-day procedure of CPP was used in this study. Morphine was administered at an effective dose of 5 mg/kg, and SCH23390 as a selective D1 receptor antagonist was administrated into the CeA. In addition, the CeA was stimulated with an intensity of the current of 150 µA. Finally, the dependence on morphine was evaluated in all experimental groups.

Findings /Results: Morphine significantly increased CPP. While the blockade of the D1 receptor of the CeA reduced the acquisition phase of morphine-induced CPP. Moreover, the combination of D1 receptor antagonist and e-stim suppressed morphine-induced CPP, even it induced an aversion.

Conclusion and implication: The current study suggests that the administration of dopamine D1 receptor antagonist into the CeA in combination with e-stim could play a prominent role in morphine dependence.

Keywords: Central amygdaloid nucleus; Dopamine D1 receptors; Electric stimulation; Morphine dependence; Rats.

INTRODUCTION

Opioids like morphine are used for relieving pain (1,2). Although, it is accompanied by side effects such as tolerance, abnormal behaviors, and addiction (3). Addiction is known as a chronic disease that causes negative psychological and physical conditions (3). The mesolimbic pathway is a main neuronal circuit in the reward system that participates in addiction (4). This pathway originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens (Nac) (5). The VTA-Nac pathway is associated with other brain areas such as the central nucleus of the amygdala (CeA) (6).

The amygdala as an important brain structure participates in regulating emotional responses such as fear (7) and anxiety (8). CeA receives efferent innervations from VTA dopaminergic neurons (9). Moreover, CeA is the major output of amygdala nuclei which plays an important role in the process of memory, learning, and emotion (10-12). Also, the role of CeA is known in the reward system (13). An experiment showed a decrement in nicotine seeking by selective inactivating of CeA neurons in addictive rats (14). Also, another document reported that the inactivation of the CeA could suppress morphine-induced preference (15).

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The dopaminergic system is the most important brain system associated with reward (16). Dopamine neurotransmitter acts *via* two superfamilies including D1-like and D2-like receptors (17). The D1-like receptors which contain the D1 receptor (D1R) and D5R stimulate and enhance intracellular levels of cyclic AMP (cAMP) (18). D2‑like receptors include D2, D3, and D4 receptors and act *via* inhibiting intracellular cAMP levels (19). The receptors are distributed in brain regions such as the NAc, the subthalamic nucleus, the striatum, the hippocampus, and the amygdaloid complex (20,21). One study has demonstrated that the administration of the D1R antagonist, SCH23390, into the hippocampus may attenuate drug‑induced conditioned place preference (CPP) (22). Additionally, the blockade of D1Rs in the basolateral amygdala (BLA) could suppress the acquisition phase of CPP induced by morphine (23).

Deep brain stimulation (DBS) is used for understanding brain function in animal models of addiction (15,24). Some animal studies have revealed that the e-stim of various brain nuclei such as NAc (25), VTA (26), and BLA (27) with high intensity could decrease drug-seeking behavior, suppress morphine-induced CPP, and reduce addiction. The mechanism of DBS activity is partially understood. DBS could alter neural activities resulting in changes in the levels of neurotransmitters such as gamma-aminobutyric acid (GABA) and dopamine (28,29).

Considering the positive effects of DBS with the high intensity of the current on brain nuclei involved in the reward system (27,30) as well as the critical role of dopamine D1Rs in the CeA (31), it seems that the effects of the combination of DBS and the antagonist of dopamine D1Rs on the CeA in morphine-induced CPP were not well understood. Therefore, this study was planned to evaluate the effect of the CeA e-stim with the intensity of the current of 150 µA alone or in combination with intra-CeA injection of SCH23390, a D1R antagonist, on morphine-induced CPP in rats.

MATERIALS AND METHODS

Animals

Male Wistar rats (Isfahan University of Medical Sciences, Isfahan, Iran) were used in this study. The animals (weighing 250-300 g) were housed in the animal room of the medical school with controlled conditions (12/12 h light/dark cycle and temperature of 20-22 ℃) and free access to food and water. They adapted to the laboratory conditions for seven days before surgery. All experimental procedures were approved by the Animal Ethics Committee of Kazeroon Azad University (Ethical No. IR.IAU.KAU.REC.1400.061) and coordinated with guidelines for the care and use of laboratory animals (National Institutes of Health Publication No. 85-23, revised 2010).

Drugs

During the current research, the agents including morphine sulfate (Temad Co., Tehran, Iran), SCH23390 (Sigma-Aldrich Co., Germany), ketamine (TRITTAU Co., Germany), xylazine (Interchemie Co., Holland), and gentamicin (Alborz Darou Co., Tehran, Iran) were used. Morphine and SCH23390 dissolved in 0.9 % saline were injected subcutaneously and intracerebrally, respectively. Also, ketamine, xylazine, and gentamicin were administered intraperitoneally.

Experimental design

Determination of response dose of morphine

To determine an effective dose of morphine, the animals under surgery were subjected to groups receiving morphine at the doses of 0.5, 2.5, 5, and 7.5 mg/kg termed as Mor 0.5, Mor 2.5, Mor 5, and Mor 7.5, respectively. In addition, a group assigned as the control group underwent surgery, but it received saline (1 mL/kg, subcutaneously) instead of morphine.

Experimental groups

After determining the effective dose of morphine, the animals under surgery were randomly assigned to the following groups (n = 6 each):

Group 1: Animals receiving saline (Sal group).

Group 2: Animals receiving morphine at the dose of 5 mg/kg (Mor group).

Group 3: Animals receiving morphine at the dose of 5 mg/kg accompanied with e-stim (Mor + St group).
Group 4: Animals receiving saline accompanied with e-stim (Sal + St group).
Group 5: Animals receiving saline accompanied with SCH23390 (0.5 µg/side) (Sal + SCH23390 group).
Group 6: Animals receiving morphine at the dose of 5 mg/kg accompanied with SCH23390 (0.5 µg/side) (Mor + SCH23390 group).
Group 7: Animals receiving saline accompanied with SCH23390 (0.5 µg/side) and e-stim (Sal + SCH23390 + St group).
Group 8: Animals receiving morphine at the dose of 5 mg/kg accompanied with SCH23390 (0.5 µg/side) and e-stim (Mor + SCH23390 + St group).

Surgery and microinjection procedure

The animals were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg). After shaving, the head of rats was fixed in a stereotaxic apparatus (Stoelting Co., USA). Then, an electrode was unilaterally implanted into the CeA according to the coordinates of anterior-posterior = -2.2 mm; medial-lateral = ± 4.2 mm; dorsal-ventral= -8.4 mm (32). Also, two guide cannulas (22 G) were bilaterally inserted at 1 mm above the CeA. After surgery, the animals were allowed to recover for one week. To prevent infection, the animals received gentamicin (6 mg/kg) for three days. After recovery, SCH23390 (31) or saline (0.5 mL/side) was bilaterally injected into the CeA for 60 s by a microinjection pump (KD scientific Co., USA), just 5 min before morphine injection.

DBS procedure

In this study, the CeA in each animal was stimulated with the intensity of the current of 150 µA with a frequency of 25 Hz once every 5 s for 10 min (Stimulator Isolator A36O, WPI, USA) just 10 min before the morphine injection. Our laboratory investigated several current intensities for reducing addiction in animal models (24,30,33), and the intensity of the current used in this study was determined according to a similar methodology used by Alaei *et al*. (26). Alaei's study showed that the e-stim of VTA by the intensity of the current of 150 µA could suppress morphine-induced CPP in male rats (26).

Behavioral Test

Apparatus

CPP apparatus consisted of three chambers (A, B, and C). Two big chambers (A and B) connected by a guillotine door were equal in size (30 cm × 30 cm × 40 cm), but not in shading and texture. The walls and floor of chamber A were black and white, whereas the ones of chamber B were white. The floors of chambers A and B were rough and smooth, respectively. The size of the chamber C was different (30 cm × 10 cm × 30 cm). In addition, it was connected to the back of chambers A and B by a guillotine door. When all guillotine doors were removed, the animal could freely move between chambers A and B through chamber C(26).

CPP procedure

In the present study, the CPP paradigm was 5 days including the phases of pre-conditioning, conditioning, and post-conditioning. These phases were 1-, 3-, and 1-day periods, respectively (15).

Pre-conditioning phase

On the first day, each animal was placed in chamber C. The animal was allowed to move freely throughout the apparatus for 15 min, and all guillotine doors were removed. Simultaneously, the time spent in chambers A and B was recorded by a digital camera system connected to the video tracking software (ANY-maze, Stoelting Co., USA). The chamber with more than 60% of the time spent by each rat was defined as a preferred chamber, whereas the opposite chamber was defined as a non-preferred chamber. Accordingly, it was planned that each animal received saline and morphine in preferred and non-preferred chambers, respectively.

Conditioning phase

From the second to the fourth day of the CPP period, the animal received morphine and saline twice a day with a 6-h interval, according to the following pattern: on days one and three, the rat

received morphine at 7:30 A.M. Then, the animal was placed in the non-preferred chamber for 45 min, and all guillotine doors were closed. After 6 h, the rat received saline and was placed in the opposite chamber for 45 min. On the third day, the animal received saline and morphine in the morning and evening, respectively.

Post-conditioning phase (testing phase)

On the fifth day, each animal was placed in chamber C. After removing all guillotine doors, the animal was allowed to move freely in the different parts of the apparatus for 15 min. The digital camera system also recorded the time spent in chambers A and B by each rat. Finally, the time spent in chambers A and B was measured by ANY-maze software. The conditioning score was measured as follows: the time spent in the morphine-paired compartment on the fifth day minus the time spent in the morphine-paired compartment on the first day (24,34,35).

Histology procedure

At the end of the experiment, all rats were anesthetized deeply. Then, transcardiac perfusion with 0.9 % saline followed by 10% formalin was performed. After dissecting, the brains were fixed in the 10% formalin solution for one week. Next, the brain sections with a thickness of 60 µm were prepared by a freezing microtome. Finally, the tissue sections were investigated by a light microscope (ERMA Co., Tokyo, Japan). Fig 1 illustrates the correct position of the electrode and cannula in the CeA.

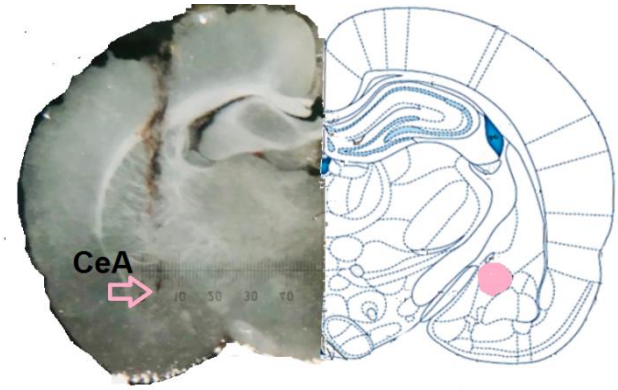

Fig. 1. The image of brain tissue demonstrating the correct position of the electrode and cannula in the CeA, magnification: ×4. CeA is, Central nucleus of the amygdala.

Statistical analysis

All data were expressed as mean ± SEM. To analyze data One-Way ANOVA followed by Tukey or Dunnett post-test was used by the SPSS statistical software version 23. *P*-values < 0.05 were considered significant.

RESULTS

Effect of morphine at different doses on the CPP

As shown in Fig 2, the statistical analysis using the Dunnett post-test revealed significant differences between the Sal group and groups receiving the various doses of morphine (F [4, 25] = 7.38; $P < 0.001$). The results showed that morphine at the doses of 5 and 7.5 mg/kg could significantly enhance the conditioning score than the Sal group. Therefore, morphine at the dose of 5 mg/kg was selected for the following investigations (Fig. 2).

Effect of the blockade of CeA dopamine D1Rs on the acquisition phase of morphine-induced CPP

There were significant differences among groups (F [3, 20] = 8.45; $P < 0.001$). The injection of morphine alone significantly increased CPP more than the Sal group. Moreover, a significant difference in the acquisition phase of CPP was observed between Mor and SCH23390 + Sal groups. Also, the administration of SCH23390 significantly inhibited morphine-induced CPP more than the Mor group, while SCH23390 in combination with saline could not change the conditioning score compared to the Sal group (Fig. 3).

Effect of the e-stim of the CeA on the acquisition phase of morphine-induced CPP

The statistical analysis exhibited significant differences among groups (F[3, 20] = 6.90; $P = 0.003$). The administration of morphine alone showed a significant increase in the acquisition phase of CPP compared to the Sal and Sal + St groups. Also, the e-stim of CeA decreased the conditioning score in the acquisition phase of morphine-induced CPP, but it was not significant (Fig. 4).

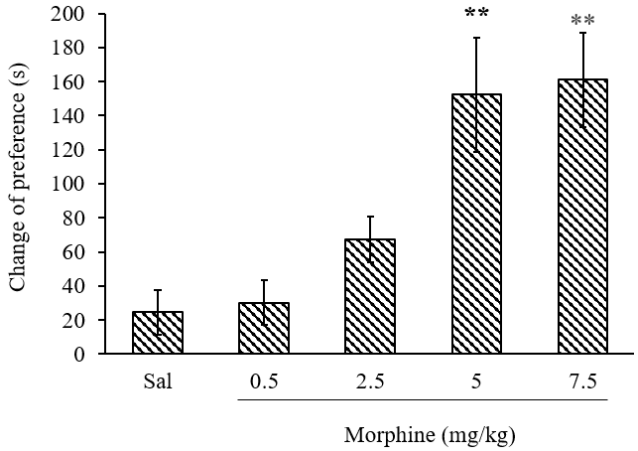

Fig. 2. Effect of morphine at different doses on the conditioned place preference in the experimental groups. The change of preference was calculated as the difference between the time spent in the morphine-paired compartment on the fifth day and the time spent in the morphine-paired compartment on the first day. Data were expressed as mean ± SEM. $^{**}P < 0.01$ Indicates the significant differences in comparison with the Sal group. Sal, Saline.

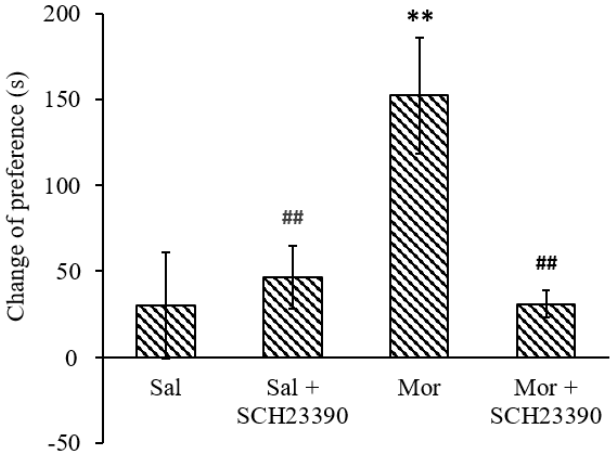

Fig. 3. Effect of SCH23390 injection on morphine-induced conditioned place preference in the experimental groups. The change of preference was calculated as the difference between the time spent in the morphine-paired compartment on the fifth day and the time spent in the morphine-paired compartment on the first day. The data were expressed as mean ± SEM. $^{**}P < 0.01$ Indicate the significant difference compared to the Sal group; $^{\#\#}P < 0.01$ versus the Mor group. Mor, Morphine; Sal, saline.

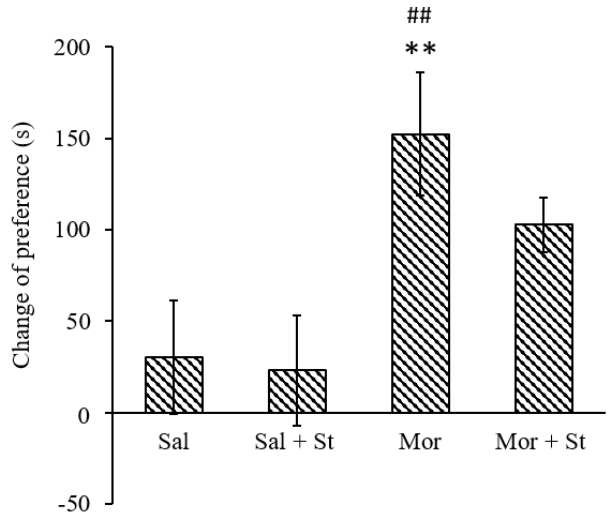

Fig. 4. Effect of the e-stim of the central nucleus of the amygdala on morphine-induced conditioned place preference in the experimental groups. The change of preference was calculated as the difference between the time spent in the morphine-paired compartment on the fifth day and the time spent in the morphine-paired compartment on the first day. The data were expressed as mean ± SEM. $^{**}P < 0.01$ Indicates the significant difference compared to the Sal group; $^{\#\#}P < 0.01$ versus Sal + St group. St, Stimulation; Mor, morphine; Sal, saline.

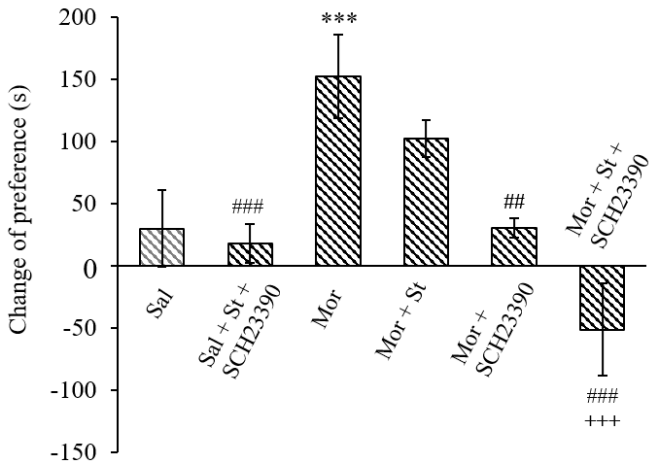

Fig. 5. Effect of the e-stim with the microinjection of SCH23390 into the central nucleus of the amygdala on the acquisition phase of morphine-induced conditioned place preference in the experimental groups. The change of preference was calculated as the difference between the time spent in the morphine-paired compartment on the fifth day and the time spent in the morphine-paired compartment on the first day. The data were expressed as mean ± SEM. $^{***}P < 0.001$ Indicates the significant difference compared to the Sal group; $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ versus the Mor group; and $^{+++}P < 0.001$ against the Mor + St group. St, Stimulation; Sal, saline.

Effect of dopamine D1Rs blockade accompanied with the e-stim of CeA on the acquisition phase of morphine-induced CPP

The results of the present study showed significant changes among the groups (F [5, 30] = 13.88; P = 0.003). The administration of morphine alone exhibited significant changes in comparison with Sal and Sal + Sch23390 + St groups. On the other hand, the e-stim of CeA had an insignificant ameliorating effect on morphine-induced CPP. Moreover, the blockade of CeA dopamine D1Rs was able to prevent the morphine-induced CPP compared to the animals receiving morphine alone, significantly. Also, the e-stim of CeA in combination with the microinjection of SCH23390 significantly reduced the morphine-induced acquisition phase compared to the Mor and Mor + St groups, even it induced an aversion effect (Fig. 5).

DISCUSSION

The current study evaluated the effects of CeA e-stim and the bilateral injection of SCH23390 into the CeA either alone or together on the acquisition phase of morphine-induced CPP in male Wistar rats. The current experiment results revealed that morphine induced a significant increase in the acquisition phase of CPP at the doses of 5 and 7.5 mg/kg. Therefore, this research used morphine at the dose of 5 mg/kg as an effective dose to evaluate the effect of DBS and blockade of dopamine D1R on morphine-induced CPP. The blockade of dopamine D1R with SCH23390 either alone or accompanied with DBS was able to prevent the acquisition phase of CPP induced by morphine, significantly.

Morphine is one of the most common analgesics to relieve acute pains, but it produces a problem in the therapeutic plan as drug abuse. Studies have demonstrated that the administration of morphine induces CPP in a dose-dependent manner (24,36,37). Morphine influences the mesocorticolimbic dopaminergic system. In this system, VTA sends the projections to the Nac. This pathway is associated with other main regions of the brain, the same as the CeA (5). Morphine acts *via* μ-opioid receptors located at the GABAergic terminals of the VTA (38). The activation of μ-opioid receptors suppresses the release of GABA and stimulates dopaminergic neurons, and subsequently releases dopamine which induces euphoria and drug dependence (39).

The current study demonstrated that the dopaminergic system of CeA could play an important role in the addictive effects mediated by morphine, particularly through dopamine D1Rs. In confirming the present results, one document reported that the intra-CeA injection of dopamine D1R antagonist decreased the acquisition phase of CPP induced by morphine (31). The inhibiting of dopamine D1Rs could ameliorate the rewarding effects of substances such as cocaine and amphetamine (40). Also, the blockade of dopamine D2Rs by ethiclopride induced an aversion effect on morphine-induced CPP (15), probably due to the various levels of D2Rs than D1Rs in the amygdala (41,42). It is documented the role of the amygdala in reward (43,44). The amygdala lesion eliminates reward-based behaviors (45). In addition, the VTA sends abundant dopaminergic (DAergic) efferents to the CeA (46), and the lesion of CeA prevents the conditioned orientation responses (47). In addition to the role of dopamine neurons in the CeA, other neurons such as GABAergic neurons also have an important role in the rewarding effect of morphine (48). The neurons regulate the activity of DAergic neurons in the VTA, and the activating and blocking of CeA GABA receptors affect opioid-induced reward behaviors (49,50).

The results of the present experiment showed that DBS alone could attenuate morphine-induced CPP, insignificantly. Some studies confirmed the findings of the current study (25,33). Some documents exhibited that the e-stim of NAc (25) and dorsal raphe nucleus (33) had an insignificant ameliorating effect on morphine-induced CPP in the acquisition phase. Although, there are conflicting observations that show the various effects of DBS on morphine-induced CPP (24,25,30). Some studies also reported the significant positive effects of DBS on attenuating morphine-induced CPP (51,52). Although, one document reported that DBS not only did not decrease morphine-induced CPP but also could

enhance it, probably due to activating the reward system and producing pleasure (33). A few documents have investigated the effect of e-stim on the CeA in addictive animal models (53). It is documented that the reward system consists of nuclei such as lateral habenular nuclei, VTA, NAc, BLA, amygdala, *etc*., and the nuclei are related to each other in the reward neuronal pathway. Thus, it seems that the issue may be involved in conflicting observations because of the position of electrodes implanted in various brain nuclei. The present study showed that the combination of DBS and dopamine D1R blockade was more effective for reducing morphine-induced CPP, even it induced an aversion effect. The e-stim of CeA induces the release of GABA, resulting in reduced DA release in the VTA and NAc (50) and subsequently decreases emotional state and memory conditioning *via* the DAergic afferents derived from the VTA (54). In addition, the blockade of dopamine D1Rs disturbed the signaling pathway of dopamine by inhibiting the conversion of ATP to cAMP and decreasing the enzyme activity of protein kinase 1 (55). It appears both DBS and SCH23390 may amplify each other effects. However, this possibility requires the next isobolographic evaluations to be confirmed. The current study did not investigate the role of dopamine D2R in combination with DBS in morphine-induced CPP. Therefore, it is recommended to address the issue in the next studies.

CONCLUSION

The results of the present study revealed that the dopamine D1Rs of CeA substantially mediate morphine dependency and addiction. In addition, the e-stim of CeA accompanied with the antagonist of dopamine D1Rs had a preventive effect on morphine dependence. The topic exhibited the presence of various neural circuits in the reward system which helps to understand and identify the different mechanisms involved in neuronal function during drug addiction. However, to achieve a better understanding of the mechanisms, more studies should be performed.

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Conflicts of Interest statement

The authors declared no conflict of interest in this study.

Authors' contribution

H. Alaei contributed to the concept, literature search, design, and definition of intellectual content; Z. Jokar carried out the literature search, experimental studies, data acquisition, data analysis, statistical analysis, preparing, editing, and reviewing the manuscript; H. Alaei, S. Khatamsaz, and, M. Shariati also edited and reviewed the manuscript. The finalized article was approved by all authors.

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