Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"
Journal Homepage: http://cjns.gums.ac.ir

Research Paper: Morphine Consumption During Lactation Impairs Short-Term Neuronal Plasticity in Rat Offspring CA1 Neurons

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Citation Aghighi F, Shabani M, Talaei SA. Morphine Consumption During Lactation Impairs Short-Term Neuronal Plasticity in Rat Offspring CA1 Neurons. Caspian J Neurol Sci. 2022; 8(2):67-75. https://doi.org/10.32598/CJNS.8.29.3

Running Title Morphine Consumption During Lactation and STP

https://doi.org/10.32598/CJNS.8.29.3

ABSTRACT

Background: Facing environmental factors during early postnatal life, directly or indirectly via mother-infant relationships, profoundly affects the structure and function of the mammals' Central Nervous System (CNS).

Objectives: This study aimed to evaluate the effect of morphine consumption during the lactation period on short-term synaptic plasticity of the hippocampal Cornu Ammonis 1 (CA1) neurons in rat offspring.

Materials & Methods: In addition to a group of control mother rats (CO), three groups subcutaneously received 5 (M5), 10 (M10), or 20 (M20) mg/kg morphine every 12 hours during the lactation period. At 45 days old, following the stimulation of the Schaffers' collaterals, basic field Excitatory Post-Synaptic Potentials (fEPSPs) were recorded in their offspring's hippocampal CA1 neuronal circuits. After the construction input/output curve, paired-pulse stimulations with the inter-stimulus intervals of 20, 80, and 200 ms were applied to determine the short-term synaptic plasticity, and the paired-pulse ratio was evaluated.

Results: The baseline synaptic responses of the rats CA1 neurons whose mothers received 10 and 20 mg/kg morphine twice daily during the lactation period decreased compared to the CO animals ($P<0.01$ & $P<0.001$, respectively). Furthermore, compared to the controls, the Paired-Pulse Ratio (PPR) of the CA1 neural circuits of M10 and M20 rats at 20 and 80 ms Inter-Stimulus Intervals (ISI) decreased ($P<0.01$).

Conclusion: Morphine exposure during the lactation period has a detrimental impact on the primary synaptic activity and short-term synaptic plasticity of the hippocampal CA1 neuronal circuits of rats' offspring.

Keywords: Morphine, Lactation, Neuronal plasticity, Hippocampus, Rats

Article info:
Received: 06 Dec 2021
First Revision: 25 Dec 2021
Accepted: 12 Feb 2022
Published: 01 April 2022

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Highlights

- Early life interferences influence postnatal brain development.
- Morphine consumption during the lactation period induces the morphine dependence of rat offspring.
- Morphine consumption during the lactation period decreases synaptic plasticity in rat offspring.

Introduction

Opioids are a group of psychoactive drugs [1]. These substances, such as morphine, codeine, and fentanyl, are common analgesics for reducing post-operative and cancer pain. Still, long-term administration of these drugs is associated with high abuse potential [2]. The result of long-term administration of morphine is changing the functions, structures, and morphology of neural systems [3, 4]. Evidence demonstrates that chronic exposure to morphine reduces neurogenesis and alters synaptic transmission in the adult hippocampus [5]. Synaptic plasticity includes Short-Term Synaptic Plasticity (STP) and Long-Term Synaptic Plasticity (LTP). Paired-Pulse Facilitation (PPF) is synaptic plasticity, i.e., short-term, activity-dependent, and common to most chemically transmitting synapses; it is expressed as an increase in the amplitude of the second of two rapidly Evoked Postsynaptic Excitatory Potentials (EPSPs) [6]. The simplest form of short-term plasticity is manifested in paired-pulse effects, i.e., delivered by consecutive pairs of stimuli; Paired-Pulse Depression (PPD) and Paired-Pulse Facilitation (PPF) [7]. Several studies indicated that chronic exposure to morphine could significantly reduce hippocampal synaptic plasticity and alter normal brain function [8, 9]. For example, Zhou et al. suggested that chronic morphine exposure significantly reduces LTP induction in the CA1 (Cornu Ammonis 1) area of the rat's hippocampus [10].

In contrast, another study reported that repeated morphine exposure enhanced LTP induction and impaired Long-Term Depression (LTD) induction at the Schaffer's collaterals to CA1 pathway without affecting the baseline synaptic responses [11]. However, despite considerable growth in our information's about the impact of chronic morphine exposure on LTP, the effect of this experience on short-term synaptic plasticity in the CA1 area of the rat's hippocampus remains indefinite. Early postnatal life experiences affect neural circuits' structure and function and cognitive function [12]. The developing brain is highly susceptible to environmental factors and stressors [13]. Scientists made several efforts to induce cognitive impairment in rodents and primates by administering various neurotoxins responsible for neurodegeneration resulting in memory loss [14]. Ghafari et al. argued that exposure to morphine before and during the gestational and lactation period induces neuronal cell death and changes the hippocampus structure in mice offspring [15]. Our previous study signified that chronic morphine exposure during the lactation period reduces spatial learning and memory and impairs LTP induction in the CA1 area of the rat offspring's hippocampus [16]. Also, Niu et al. indicated that exposure to morphine during the pregnancy impairs the rat offspring's spatial memory and synaptic plasticity of dentate gyrus neurons. It seems that reduced GABAergic inhibition plays a role in these effects [17].

Furthermore, studies outlined that Gamma-Aminobutyric Acidergic (GABAergic) synaptic transmission is influenced by morphine [18, 19]. As per evidence, GABAergic inhibition plays an essential role in learning and memory processes [20] and their probable related mechanism, synaptic plasticity [21]. Plenty of GABAergic interneurons is nested in the hippocampus [22]. Maroun and Richter-Levin reported that the GABAergic system had been implicated in short-term hippocampal plasticity [23]. This study aimed to evaluate the effects of morphine exposure during the lactation period on the modulation of short-term synaptic plasticity in the neural circuits of rats' hippocampal CA1 area.

Materials and Methods

Forty male Wistar rats aged 45 days (120-150 g) were used in this experimental study. The examined rats were housed in a standard animal house at temperature 20-22°C, air humidity 50%-55%, and a 12-12 h light-dark cycle. The animals had access to food and water ad libitum. All experiments were authorized by the Ethical Committee of Kashan University of Medical Sciences, Kashan, Iran, also conducted per the Directive 2010/63/EU on protecting animals used for scientific purposes. The examined animals were divided into one Control

group (CO) and 3 groups of rats whose mothers received 5 (M5), 10 (M10), or 20 (M20) mg/kg morphine every 12 hours during the lactation period, subcutaneously. All the rats were deprived of milk on day 21 after the birth. Besides, only two offsprings were picked from each morphine-received mother. Two hours after the last dose of morphine was administered to the mothers, we studied the withdrawal syndrome symptoms in the offspring. The animals were tested by the Intraperitoneal (IP) injection of 2 mg/kg Naloxone hydrochloride (Temad, Iran). Immediately after the injection, rats' behavior signs were observed for 30 min according to a modified version of the Gellert–Holtzman scale in a Plexiglas chamber (30×30×50 cm). The signs were included the graded (body weight loss during 24 hours after the injection, jumps, abdominal contractions, & wet dog shakes) and the checked signs (irritability, writhing, diarrhea, ptosis, erection, or genital grooming, & teeth chattering) [24].

In vivo Electrophysiology

To record field Excitatory Post-Synaptic Potentials (fEPSPs), the rats were anesthetized with urethane (1.5 g/kg, IP) and placed in a stereotaxic apparatus (Borj Sanat, Iran). According to Paxinos and Watson stereotaxic atlas [25], a bipolar stimulating electrode was implanted into the Schaffer's collaterals (4.2 mm posterior to bregma, 3.8 mm lateral to the midline, & 2.8 mm below the skull), and a monopolar recording electrode was lowered to the CA1 stratum radiatum (3.4 posteriors to bregma, 2.5 mm lateral to the midline, and 2.5 mm below the skull). Electrodes were prepared from Teflon-coated stainless-steel wire (0.008-inch diameter, A-M Systems, USA) exposed only at the tip (tip separation 0.10 mm). The proper location of the electrodes was determined by optimizing the evoked response. Using the eLab system (ScienceBeam, Iran) and related computer software (eProbe), fEPSPs were recorded from the stratum radiatum of the CA1 area of the hippocampus in response to stimulation (two sweeps/min at 30-sec intervals) of the ipsilateral Schaffer's collaterals. Recording signals were amplified by the eLab amplifier and saved at a 10 kHz sampling rate for offline analysis. Electrical stimulation consisted of constant current rectangular pulses (200 µs, 0.1 Hz, 50–1000 µA) delivered by the eLab isolator. The baseline recording was considered stable when the fEPSP amplitude variation (mV) was less than 10% for at least 20 min. The animals with unstable baseline responses were discarded from the experiments. By increasing the stimulus intensity and measuring the amplitude of the fEPSPs, an Input/Output (I/O) curve was set. The evoked field potentials were measured at five different stimulation intensities, and I/O curves were constructed. The threshold intensity (T) was the lowest intensity that evoked a measurable response. Then, 2T to 5T stimulus intensities were applied. Stimulus intensity was adjusted to provide a response that was 60% of the maximum response as a test pulse. Investigating the Short-Term Synaptic Plasticity (STP), after 30 min stable baseline recording, paired-pulse stimuli were applied at 20, 80, and 200 ms Inter-Stimulus Intervals (ISI).

The collected data were expressed as mean±SEM. Using one-way Analysis of Variance (ANOVA), the Gellert–Holtzman scores of the study groups were analyzed. The averaged waveform of each six fEPSPs was used for statistical analysis. The extent of changes (%) in fEPSPs slope (mV/ms) was normalized concerning the 30 min baseline recording and then was analyzed by ANOVA. Tukey's test was applied as a post-hoc examination. All statistical analyses were performed in SPSS at $P<0.05$.

Results

Our results demonstrated that receiving morphine during the lactation period induces the morphine dependence of rats' offspring, demonstrating withdrawal signs. The overall Gellert-Holtzman score by one-way ANOVA data indicated a significant difference between the study groups ($F_{3,36}=14.423$; $P<0.0001$). The overall mean±SEM Gellert-Holtzman score of M5 rats was 10.34±2.76 (Figure 1) and increased to 19.67±5.08 and 22.33±3.68 in M10 and M20 groups, respectively. According to Tukey's test data, there was a significant difference between the CO group and the other groups ($P<0.001$); also between the M5 group and M10 and M20 groups ($P<0.01$, for both comparisons).

Stimulating Schaffer's collaterals, evoked responses were recorded from hippocampal CA1 neurons of rats' offspring. Six sweeps were averaged at each stimulus intensity. The slope of fEPSPs was calculated at 5 different stimulus intensities, and then input-output curves for the study groups were created. One-Way ANOVA results signified a significant difference between the experimental groups in the mean values of stimulus intensity ($F_{3,36}=4.036$; $P<0.001$). According to Table 1, the mean stimulus intensity required for evoked responses in the M10 and M20 groups was significantly greater than the CO animals ($P<0.01$ for both comparisons per set of stimulus intensity). Furthermore, the statistical analysis of the slope amplitude of fEPSPs in each stimulus intensity demonstrated a significant difference between the

Table 1. The mean±SEM values of different stimulus intensity (µA) in the experimental groups

Groups	Mean±SEM				
	T	2T	3T	4T	5T
CO	95.48±5.15	181.61±10.84	315.66±14.38	449.68±17.84	552.09±28.49
M5	101.51±7.24	179.36±11.41	334.76±16.21	472.42±21.03	601.35±21.76
M10	119.58±6.38**	217.84±15.12**	383.37±18.49**	688.94±14.67**	731/66±19.64**
M20	138.22±9.53**	246.92±18.32**	491.17±11.13**	716.45±22.39**	839.08±27.18**

The threshold intensity (T) was the lowest intensity that evoked a measurable response, and the other applied intensities were 2T to 5T.

** P<0.01; the CO vs. the M10 and M20 groups.

evoked responses ($F_{3,36}$=3.719; P<0.001). As illustrated in Figure 2, receiving morphine during the lactation period caused a significant decrease in the baseline synaptic responses of the offsprings' CA1 neurons, dose-dependently.

The paired-pulse stimulation paradigm was applied to evaluate the effect of morphine exposure during the lactation period on the excitability of the hippocampal neuronal circuits of rats' offspring. The one-way ANOVA results outlined a significant difference between the Paired-Pulse Ratio (PPR) of different study groups at 20 and 80 ms Inter-Stimulus Intervals (ISI) ($F_{3,36}$=7.652; P<0.001 & $F_{3,36}$=11.839; P<0.001, respectively). There was no significant difference between the PPR of different study groups at 200 ms ISI (Figure 3). The mean±SEM PPR of the CO animals at 20 ms ISI was 92.44±2.98% and significantly decreased to 77.11±3.48% and 70.76±5.93% in the M10 and M20 groups (P<0.01 for both the comparisons). Tukey's results also suggested that the PPR of the mean±SEM CO animals at 80 ms ISI was 151.33±8.73% and significantly decreased to 129.38±9.37% and 123.82±12.62% in the M10 and M20 groups (P<0.01 for both the comparisons).

Discussion

We reported that morphine consumption during the lactation period causes morphine dependency in rat off-

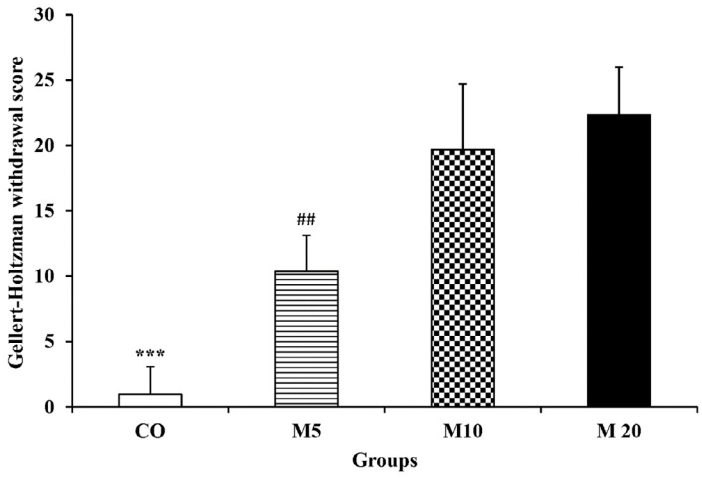

Figure 1. Histograms show the effect of receiving different doses of morphine during the lactation period on the dependency of rat offspring

The one-way ANOVA data indicated that the overall Gellert-Holtzman score grew as the morphine dose increased. Data are presented as Means±SEM.

*** P<0.001 the CO group vs. the other groups.

P<0.01 the M5 group vs. the M_{10} and M_{20} groups.

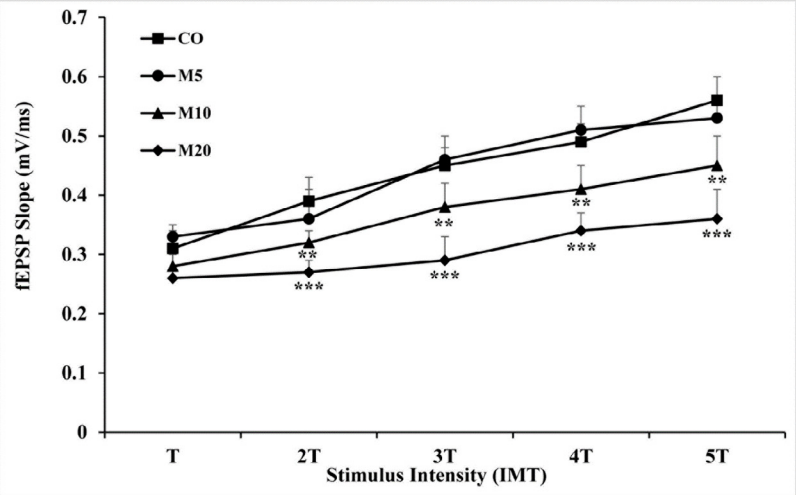

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Figure 2. The synaptic input/output (I/O) relation between the Schaffer's collaterals and CA1 pyramidal neurons in the hippocampus of offspring in different study groups

Receiving morphine during the lactation period caused a significant decrease in the baseline synaptic responses of the offsprings' CA1 neurons, dose-dependently.

** P<0.01 the CO group vs. the M10 group in each stimulus intensity.

*** P<0.001 the CO group vs. the M20 group in each stimulus intensity.

spring. We also demonstrated that besides decreasing the basic synaptic responses, short-term synaptic plasticity of the rats CA1 neurons whose mothers received 10 mg/kg and 20 mg/kg morphine twice daily during the lactation period significantly decreased at 20 and 80 ms ISI. There has often been discussion about whether morphine received by the mother can be detected in breastfed babies or not. According to our information, no investigation on the excretion of morphine in animals' breast milk was published. Still, Feilberg et al. demonstrated that morphine is detected in human milk only 30 minutes after injection. They also concluded that morphine concentrations are higher in milk than in plasma [26]. Robieux et al. have revealed that 0.8 to 12% of morphine received by the mother can be found in the serum of a breastfed infant [27].

Besides, Tao et al. stated that the intake of morphine during pregnancy and lactation makes 14-day-old rat offspring dependent and reduces the anti-nociceptive morphine effect [28]. At the molecular level, Yang et al. reported that the pre- and post-natal morphine exposure influences the N-Methyl-D-Aspartate (NMDA) receptors-mediated synaptic plasticity in the hippocampus of rat offspring [29]. Our previous study showed that morphine consumption during the lactation period causes morphine dependency, impairs spatial learning and memory, and also decreases synaptic plasticity of hippocampal neural circuits of rat offspring [16]. As a kind of brain disorder, drug dependence alters the function of the neuronal circuit, including altering neuronal plasticity and synaptic transmitter release [30, 31]. Furthermore, the drug's chronic administration leads to toxicity due to the drug overdose and increased side effects [32]. A study suggested that addiction is an aberrant form of memory associated with synaptic plasticity transformation [33].

Furthermore, morphine dependence affects the plan of a synaptic junction [4, 34]. For example, acute exposure to morphine could alter the strength of present connections that might lead to changes in short-term plasticity [35]. Paired-Pulse stimulation elicited by two similar stimuli is a procedure to study short-term plasticity, i.e., substantial in information processing [36]. Wang et al. found that chronic morphine exposure significantly reduces PPD and frequency depression in rats' primary visual cortex [35]. These authors previously reported that postsynaptic GABAergic inhibition might be vital for short-term depression in the geniculo-cortical pathway.

Moreover, the GABAergic system is essential for short-term synaptic plasticity [37]. For example, the PPD of field potentials could be induced by normal feedforward or feedback inhibitory influences [38]. The blockade of GABAergic inhibition by GABAA receptors' antagonists can increase PPR or turn the PPD to PPF [39]. Additionally, variation in presynaptic calcium

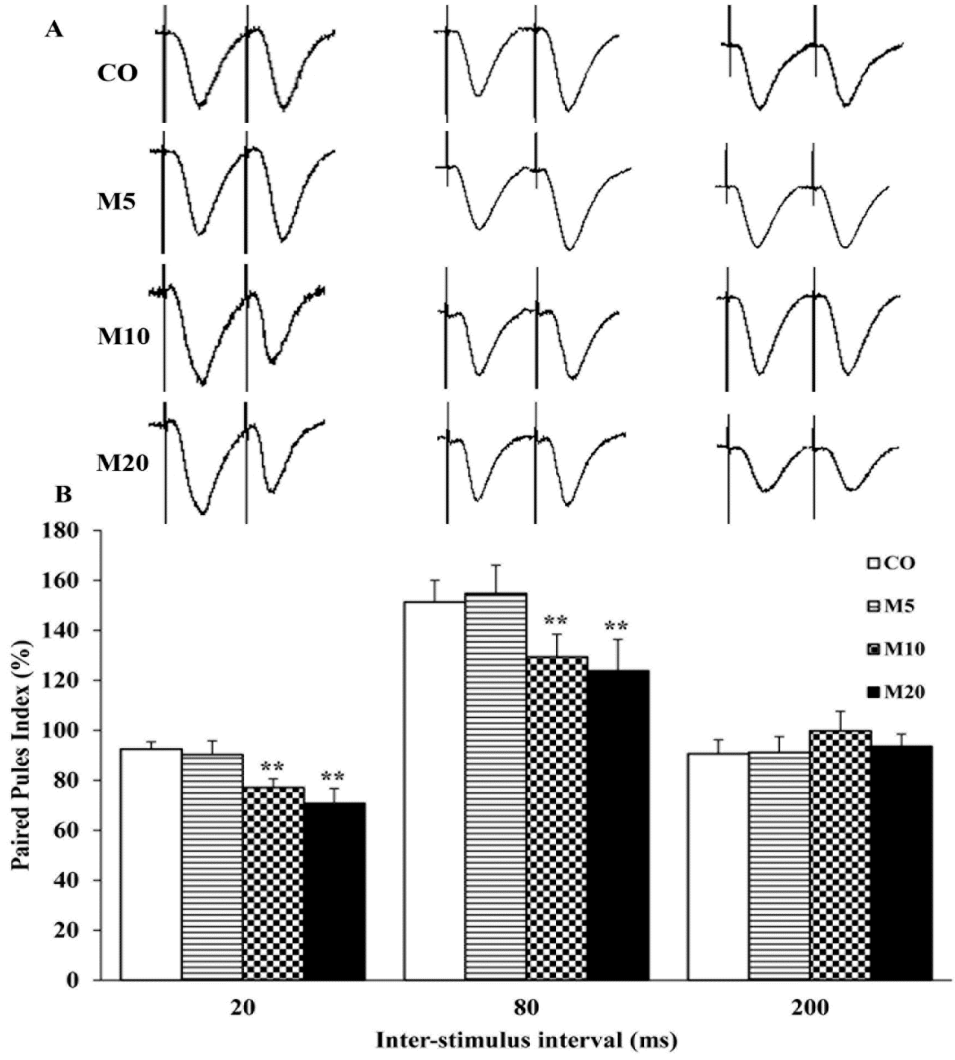

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Figure 3. A: Representative traces of fEPSPs were recorded from the hippocampal CA1 area of rats in each study group at different ISI; B: Paired Pulse Ratio (PPR) at 20, 80, and 200 ms inter-stimulus interval of the evoked responses recorded from the hippocampal CA1 neurons of different study groups

Morphine exposure during the lactation period caused a significant decrease in the PPR of the offsprings' CA1 neural circuits at 20 and 80 ms ISI.

**P<0.01 the CO group vs. the M10 and M20 groups in 20 ms ISI.

##P<0.01 the CO group vs. the M10 and M20 groups in 80 ms ISI.

[7], i.e., responsible for PPF, other mechanisms, such as desensitization of AMPA receptors [40] and GABAergic inhibition [39], are implicated in the organization of PPD. Zhang et al. reported that Glycine receptors affect short-term hippocampal plasticity by influencing GABAA receptors-mediated synaptic currents [37]. As a part of the limbic system, the hippocampus plays an essential role in synaptic plasticity and neural adaptation in the CNS. It has multiple opiate receptors and GABAergic neurons [41]. Central GABAergic neurotransmission has interconnected with the mesolimbic dopaminergic system during addiction processes [42]. It was suggested that μ-opioid receptors connected two GABAergic and opioidergic systems [43]. The result of chronic morphine exposure is the downregulation of ionotropic GABAB receptors in the mice [44]. Morphine treatment has also been shown to decrease GABA release [45], increase GABA uptake, and elevate GABA transporters expression in the hippocampus [46]. Zarrindast et al. reported that GABAergic receptors in the CA1 region of the hip-

pocampus have a vital role in the restoring effect of morphine on the impairment of memory induced by morphine [47]. On the other hand, activating GABAA and GABAB receptors with microinjections of their agonists into the dorsal hippocampus inhibited morphine reward [48, 49]. Therefore, morphine consumption in the hippocampal CA1 neurons of rat offspring can disrupt short-term synaptic plasticity during the lactation period by weakening GABAergic inhibition.

Conclusion

Morphine exposure during the lactation period has a detrimental impact on the basic synaptic activity and short-term synaptic plasticity of the hippocampal CA1 neuronal circuits of rat offspring.

Ethical Considerations

Compliance with ethical guidelines

All study procedures complied with the ethical standards outlined in the Helsinki Declaration (2013). The Ethical Committee of Kashan University of Medical Sciences, Kashan, Iran approved this study (Code: IR.KAUMS.MEDNT.REC.1396.82).

Funding

This research was supported the Deputy of Research and Technology, Kashan University of Medical Sciences, Kashan (Grant no: 96160).

Authors contributions

Conceptualization and methodology: All authors; Investigation: Mohammad Shabani; Writing - original draft: Fatemeh Aghighi and Mohammad Shabani; Writing - reviewing & editing, funding acquisition, supervision: Sayyed Alireza Talaei.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors thank KAUMS Animal Breeding Center for supplying the animals and Miss Asma Vatankhah for her assistance in data collection.

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