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Original article

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Memantine, A NMDA Receptor Inhibitor Attenuate Lipopolysaccharide-Induced Lung Inflammation and Oxidative Damage in Mice

Atlas Gholami[1], Mahmoud Hosseini [2], Mohammad Hossein Boskabady[1, 3], Masoumeh Gharib[4], Zahra Gholamnezhad*[1, 3]

Abstract

Background: The anti-oxidative and anti-inflammatory effect of memantine (an N-methyl-D-aspartate receptor inhibitor) has been shown. Therefore, the present study aimed to evaluate the preventive effects of memantine against lipopolysaccharide (LPS)-induced sub-acute lung injury in mice.

Methods: Male C57BL/6 mice (n=30) were randomized in five groups as follows: (1) control (saline containing 10% DMSO); (2) LPS (5 mg/kg, intraperitoneally); and (3, 4, and 5) LPS 5 mg/kg + memantine 5, 10, 20 mg/kg, respectively. Memantine (dissolved in 10% DMSO) was administrated orally three days before the LPS injection and continued for three days after injury induction. Finally, the levels of markers of oxidative stress, malondialdehyde (MDA), catalase (CAT) and superoxide dismutase (SOD), interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), and nitric oxide (NO), were measured and histopathological changes in the lung tissue were assessed.

Results: Lipopolysaccharide (LPS) administration increased the TNF-α, IL-1β, NO, and MDA, levels, while decreasing the lung tissues activity of CAT ($P< 0.05$) and SOD ($P< 0.001$) and caused lung pathological damages. Memantine 20 mg/kg, alleviated LPS-induced injury score, reduced the lung tissue levels of TNF-α, IL-1β, MDA, and NO, and restored CAT activity ($P< 0.05$, $P< 0.01$).

Conclusion: LPS-triggered elevation of lung injury markers including histopathological changes, inflammatory cytokines, and oxidative damage. All pathological changes were suppressed by memantine.

Keywords: Inflammation, Lipopolysaccharide, Lung Injury, Memantine, Oxidative stress.

Introduction

Inflammatory processes act as a protective defense against several destructive stimuli and help the organs to repair, however uncontrolled inflammation can induce many chronic diseases (1). Moreover, the elevation of reactive oxygen species (ROS) might induce tissue injury and activate inflammatory processes, which worsen the situation (2). Irritants, air pollutants, and allergens might cause inflammation in the lung, trigger the development of a variety of pulmonary diseases and deteriorate respiratory function in idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), and asthma. Lung injury might be acute or chronic according to the duration and intensity of toxin exposure (1). Inflammation can develop acute lung injury (ALI) as a destructive disorder, which can cause hypoxemic respiratory failure, protein-rich pulmonary edema, other morbidities, and even death (3-5). The incidence and mortality

1: Department of Physiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
2: Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
3: Applied Biomedical Research Center, Basic Sciences Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
4: Department of Pathology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
***Corresponding author: Zahra Gholamnezhad; Tel: +98 5138002236; E-mail: gholamnezhadz@mums.ac.ir.**
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rate of ALI is high, and 10% of admissions in all intensive care units and 4% of all hospital admissions are due to acute respiratory distress syndrome (ARDS) and/or ALI. Despite recent clinical advancements, ALI patients' mortality rate remains as high as 30-40%, and it is still a high-burden condition with no effective treatment (4).

It has been shown that systemic or local exposure to lipopolysaccharide (LPS) might induce acute inflammation in the lungs. Therefore, LPS is commonly used to induce lung injury in rodents to provide an ARDS animal model and to provoke the lung to show neutrophil-mediated inflammation similar to that ARDS patients (6). When LPS is used locally, it can acutely provoke inflammatory cells to migrate into the pulmonary tissue, increase permeability in pulmonary capillaries, and cause interstitial and alveolar tissue edema (7), and oxidative stress (2). In addition, LPS might induce cell infiltration in pulmonary tissues by increasing secretion of tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β via nuclear factor kappa B (NF-κB) signaling pathways, and it can activate the host Toll-like receptor 4 (TLR4) to promote the inflammation (6, 8). Moreover, an *in vitro* study reported that the stimulatory effects of LPS on *TNF-α* expression by macrophages are mediated via t NF-κB and certain inflammatory miRNAs (9).

The N-methyl-d-aspartate (NMDA) receptor is expressed in the rat lung and alveolar macrophages (10). The NMDA receptor (NMDAR) in the pulmonary tissue mediates glutamate-induced excitotoxic effects, and glutamate can play a role in inflammation and constriction of the lung airways (11). Activation of NMDAR can lead to an elevation of intracellular calcium, upregulation of neuronal nitric oxide synthase (nNOS), mitochondrial dysfunction, production of reactive oxygen species (ROS), elevation of endoplasmic reticulum stress, and and the release of lysosomal enzymes (12). Memantine, an NMDAR antagonist, can attenuate lung inflammation by reducing glutamate release, Ca2+ influx, macrophage activation induced pyroptosis, and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) phosphorylation (11, 13). Memantine might suppress the pathogenicity and virulence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and can play a beneficial role in preventing pulmonary and brain damage (14). Moreover, memantine nitrate (MN-08), can act as an NMDAR antagonist of and release NO. It could ameliorate LPS-mediated sepsis in mice by balancing systemic immune dysfunction and inflammatory processes, and diminish pulmonary inflammatory infiltration and damage. In addition, the anti-inflammatory effects of memantine in chronic hepatitis C and in sepsis-induced neuroinflammation by LPS have been demonstrated (15). Moreover, it has been demonstrated that memantine reduces the expression of IL-8 and IL-6 prevents oxidative damage and mitochondrial dysfunction by rescuing membrane potential and decreases ROS production via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-4 (NOX-4). Memantine could also suppress pro-inflammatory cytokines (IL-1β, and TNF-α), and reduce glutamate release, modulate the activation of NMDAR1 in the spinal cord and alleviate pain indicators in diabetic mice (16).

Regarding the antioxidative and anti-inflammatory effects of memantine, the aim of the present study was to evaluate its efficacy against LPS-induced subacute lung injury in mice in order to identify a potential treatment for ALI.

Materials and Methods

Animals

Thirty male C57BL/6 mice were obtained from the animal house of Mashhad University of Medical Sciences., 25 ± 5 g) C57 mice were supplied. The animals were randomly divided and housed (six per cage) in a standard situation (12/12 h light/dark cycle, 22 ± 2 ℃) with free access to water and standard rodent chow. The experimental protocols were approved by the Biomedical Research Ethics Committee of

Mashhad University of Medical Sciences (Approval code: IR.MUMS.AEC.1402.021).
Materials and drugs Memantine hydrochloride was obtained from Tasnim Pharmaceutical (Tehran, Iran), LPS from Sigma (Escherichia coli serotype O55:B5; Millipore Sigma, USA), Griess Reagent from Promega corporation (Madison, USA), xylazine from Bioveta company (Ivanovice, Czech Republic), and ketamine (10%) from Bremer Pharma GmbH (Warburg, Germany). For biochemical assessments, other chemical agents, including thiobarbituric acid (TBA), dimethyl sulfoxide (DMSO), pyrogallol, Ellman's reagent, hydrogen peroxide (H2O2), and ethylenediaminetetraacetic acid (EDTA) were purchased from Merck Company (Darmstadt, Germany).

Experimental design

Animals were randomly divided into 5 groups as: control (received sterile saline containing 10% DMSO as the vehicle of LPS and memantine), LPS (received LPS on day 4 of the experiment), and three groups Mem5, Mem10, and Mem20 that respectively received memantine 5, 10, and 20 mg/kg from 3 days before the injection of LPS and induction of sepsis until 3 days after that. DMSO 10% was used to dissolve memantine, and the above-mentioned doses were administered daily through oral gavage. On day 4 of the study, one hour after the memantine administration, sepsis and lung injury were induced by intraperitoneal (i.p.) injection of LPS (dissolved in sterile saline) at a dose of 5 mg/kg (17, 18). Finally, the mice were deeply anesthetized by injections (i.p.) of a mixture of xylazine (12.5 mg/kg) and ketamine (80 mg/kg) and euthanized. Then, the chest was opened, and the lung tissue was harvested and divided into two parts. One part was kept at -20 ℃ for biochemical assessment and the other in formalin for histopathological evaluation. For biochemical assessments, the level of metabolites of nitric oxide (NO), cytokines (IL-1β and TNF-α), the activity of catalase (CAT) and super oxidedismutase (SOD), and malondialdehyde (MDA) were evaluated.

Biochemical Assessment

The lung tissue samples (100 mg) were homogenized in a chilled phosphate buffer (50 mM, pH 7.4) using an ultrasound homogenizer. Then, the supernatants were isolated by centrifuging 10 min at 5000 rpm and used for cytokine assay and oxidative stress measurements.

Evaluation of cytokines and NO

The ELISA kits for mice (IL-1β and TNF-α) were used as per the instructions of the manufacturer (Karmania, Pars Gene, Iran) to determine lung inflammatory cytokine levels. Using the Griess reagent kit, the NO metabolites were analyzed based on the reaction between N-1-naphthylethylenediamine dihydrochloride and sulfanilamide solutions, which were assayed at 520 nm (19).

Evaluation of oxidative stress

The MDA, as a marker of lipid peroxidation was quantified based on the reaction with TBA. The supernatant was mixed with TBA solution (5 M HCl, 40% trichloroacetic acid (TCA), and 2% TBA), then warmed for 45 min in boiling water and centrifuged for 10 min at 1000 × g; finally, at 535 nm, the supernatants' absorbance was read (19).

The colorimetric method of Madesh was used to determine the superoxide dismutase (SOD) activity (20).

The Aebi method was used for the evaluation of catalase (CAT) activity, which was quantified based on the consumption of H2O2 monitored by spectrophotometry (19).

Histopathological analysis

The fresh upper left lungs were isolated (n = 6 per group) and fixed in n 10% buffered formalin solution. Then the sections (4 μm thickness) were stained with hematoxylin and eosin (H&E). The pathological score was determined as previously noted (11).

Statistical analyses

The data are presented as mean ± standard error of the mean (SEM) and analysis was done using version 22 of SPSS software. The

Kolmogorov–Smirnov test was done to check the data normality. A one-way ANOVA comparison test followed by a Tukey's post hoc test was used to compare the means of biochemical parameters. A P< 0.05 was considered statistically significant.

Results

The influence on inflammatory cytokines

Based on Figures 1A and B, IL-1β and TNF-α levels in lung tissue were higher in the LPS group compared to the control group (P< 0.01 and P< 0.05, respectively). Administration of memantine (all three doses) reduced lung tissue IL-1β level, dose-dependently compared to the LPS group (P< 0.05 and P< 0.01, respectively). However, only 20 mg/kg memantine significantly decreased TNF-α level compared to the LPS group (P< 0.01). The levels of TNF-α in the Mem5 and Mem10 groups were not significantly different from the LPS group (Fig. 1).

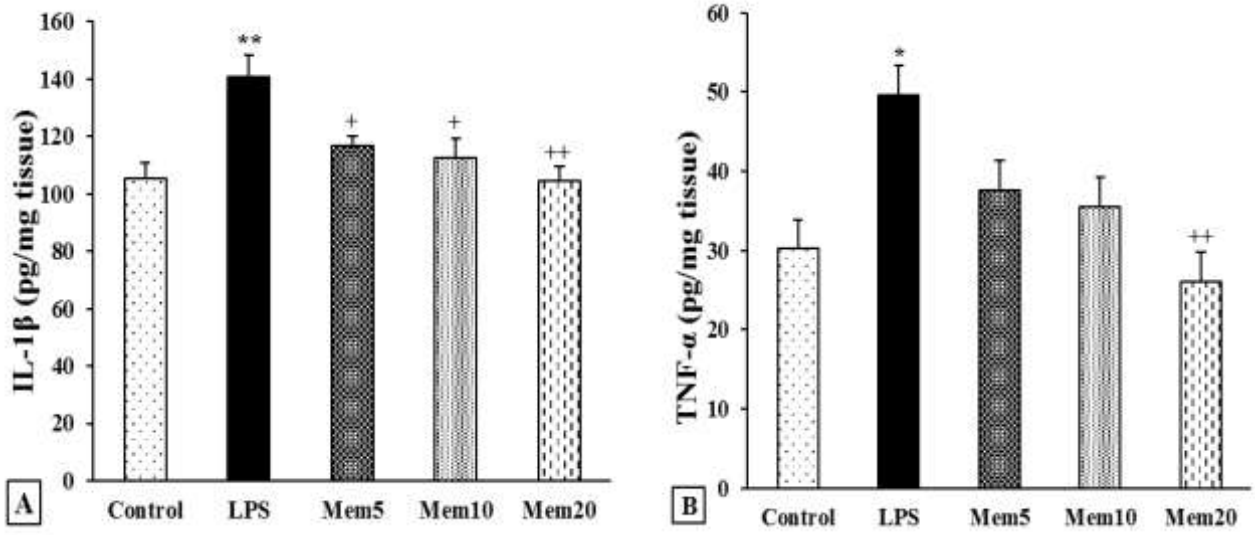

Fig. 1. The lung tissues IL-1β (A) and TNF-α (B) levels in the control, lipopolysaccharide (LPS), LPS + memantine 5 mg/kg (Mem5); LPS + memantine 10 mg/kg (Mem10) and LPS + memantine 20 mg/kg (Mem20) groups. *P< 0.05 and **P< 0.01 show a significant difference compared to the control group. $^{+}$P< 0.05 and $^{++}$ P< 0.01 show significant differences compared to the LPS group. The results are expressed as mean ± SEM (n= 6 in each group). One-way ANOVA followed by Tukey's multiple comparison test was applied for statistical analysis among the groups.

The influence on NO metabolite and MDA levels

In the LPS group, the level of NO metabolites was higher than that of the control animals (P< 0.05). Animals' treatment with memantine 20 mg/kg significantly reduced the level of NO metabolites in comparison with the LPS group (P< 0.05; Fig. 2A).

A significant increase in the MDA level of lung tissue following LPS injection (P< 0.01) was seen. The lung MDA level in the Mem5 group was also higher than that of the control animals (P< 0.05). However, the MDA level was reduced in the Mem20 group in comparison with the LPS group (P< 0.05; Fig. 2B).

The influence on CAT and SOD activity

As indicated in Figures 3A and B, CAT and SOD activity in the lung tissue of the LPS group was less than that of the control animals (P< 0.001 for both). Pretreatment of animals with memantine did not improve CAT and SOD activities and these values were still lower than those of the control animals (P< 0.01-P< 0.001). Only pretreatment with memantine 20 mg/kg improved CAT activity in comparison with the LPS group (P< 0.05).

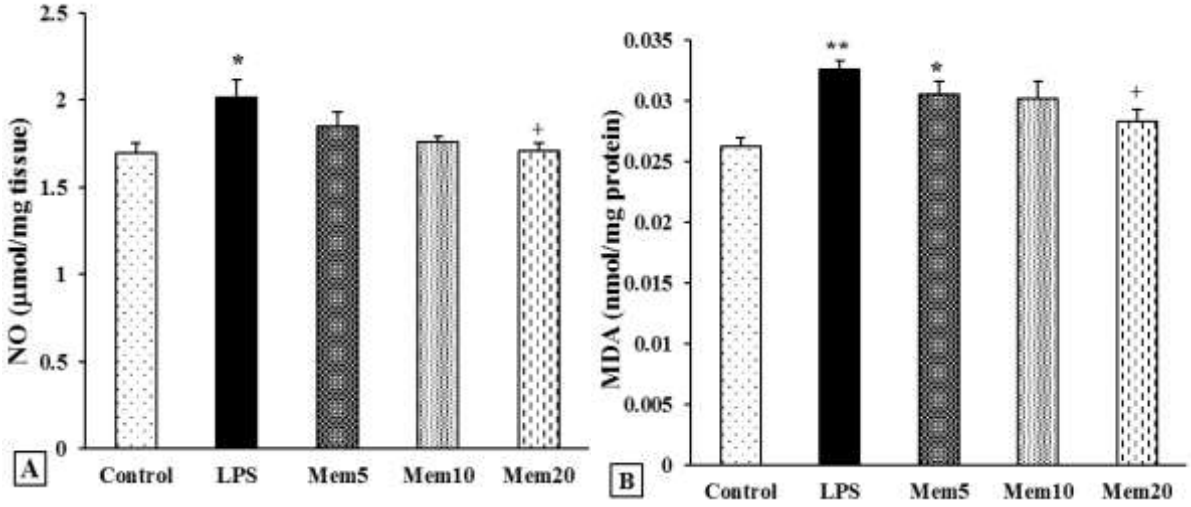

Fig. 2. The lung tissue NO metabolite (A) and MDA levels (B) in the control, lipopolysaccharide (LPS), LPS + memantine 5 mg/kg (Mem5); LPS + memantine 10 mg/kg (Mem10), and LPS + memantine 20 mg/kg (Mem20) groups. *P< 0.05, and **P< 0.01 show a significant difference compared to the control group. $^{+}$P< 0.05 shows a significant difference compared to the LPS group. The results are expressed as mean ± SEM (n= 6 in each group). One-way ANOVA followed by Tukey's multiple comparison test was applied for statistical analysis among the groups.

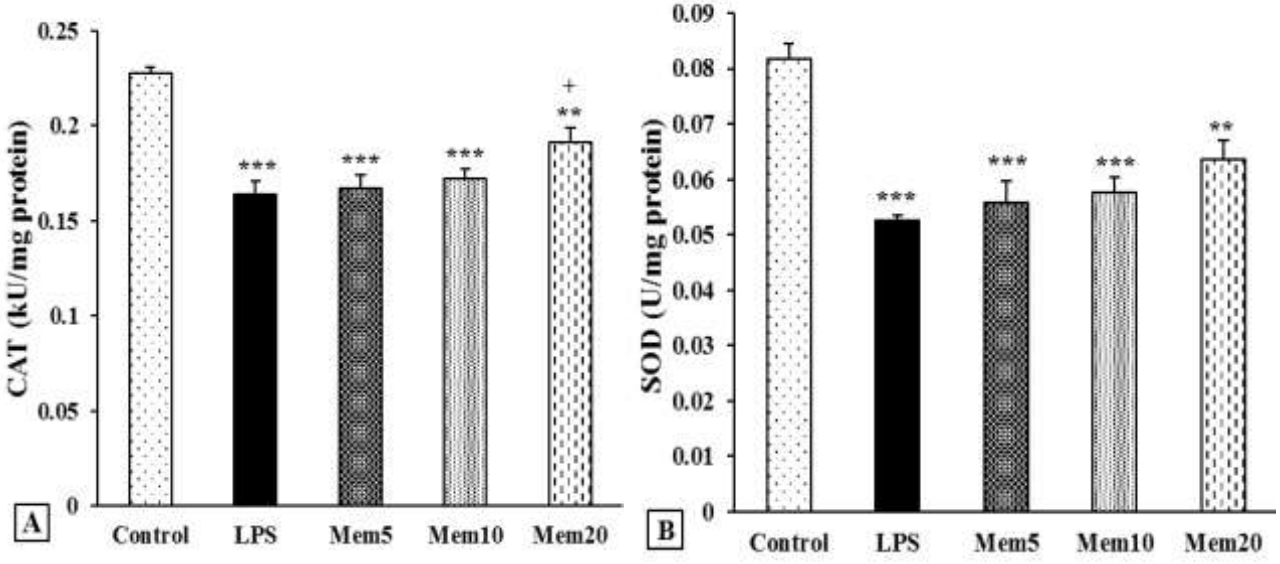

Fig. 3. The lung tissue CAT (A) and SOD activity (B) in the control, lipopolysaccharide (LPS), LPS + memantine 5 mg/kg (Mem5); LPS + memantine 10 mg/kg (Mem10), and LPS + memantine 20 mg/kg (Mem20) groups. **P< 0.01 and ***P< 0.001 show a significant difference compared to the control group. $^{+}$P< 0.05 shows a significant difference compared to the LPS group. The results are expressed as mean ± SEM (n= 6 in each group). One-way ANOVA followed by Tukey's multiple comparison test was applied for statistical analysis among the groups.

*The influence on lung histo*pathology

In the LPS group, histopathological evaluation showed polymorphonuclear (especially neutrophil) infiltration, edema, congestion, accumulation of protein debris, and elevation of injury score (Fig. 4). Although the memantine groups had lower injury scores in comparison to the LPS group, only the Mem20 group showed statistically significant improvement (P< 0.05).

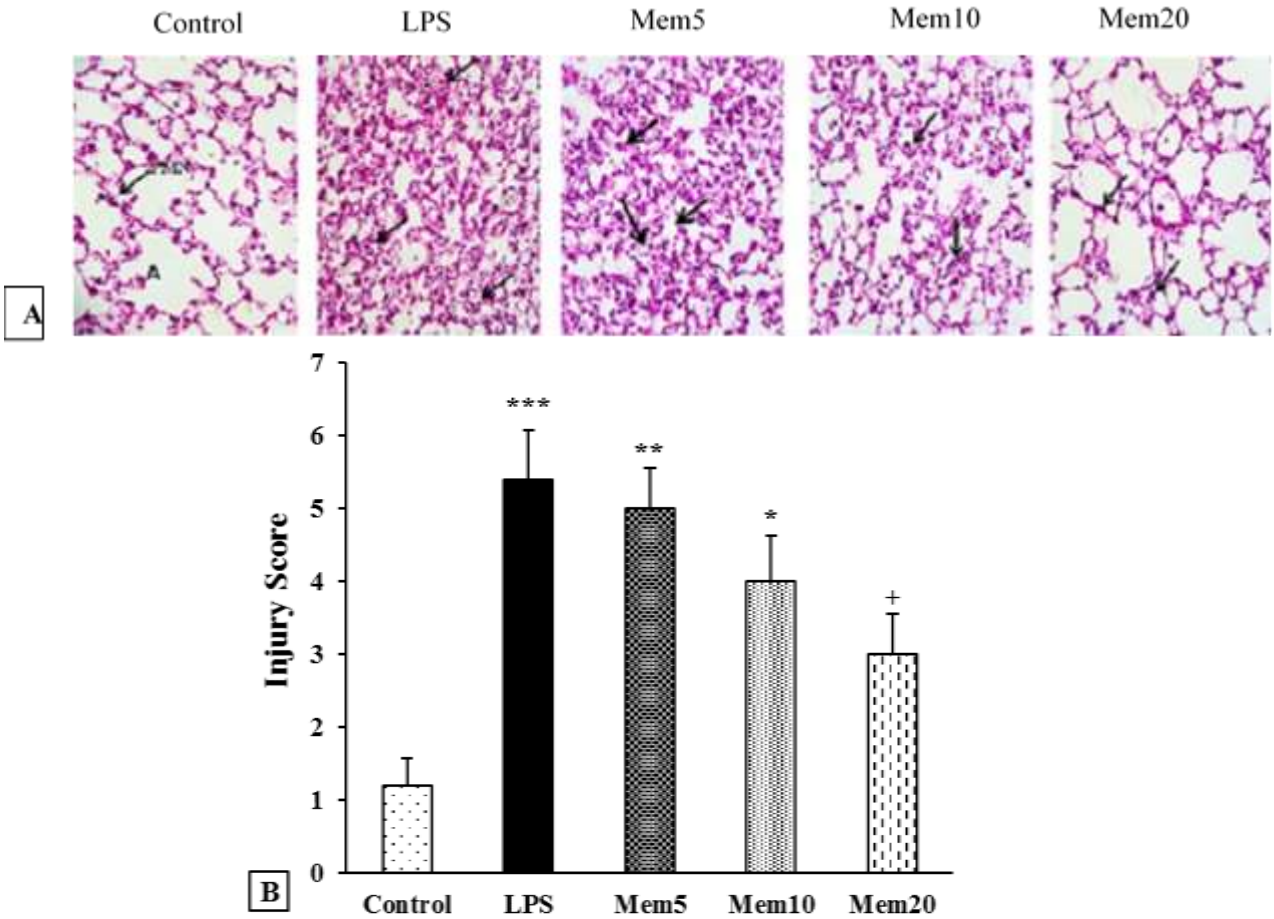

Fig. 4. Lung histological staining (H&E, ×40) (A) and the injury score (B) in the control, lipopolysaccharide (LPS), LPS + memantine 5 mg/kg (Mem5); LPS + memantine 10 mg/kg (Mem10) and LPS + memantine 20 mg/kg (Mem20) groups. Black arrows indicate polymorphonuclear (PMN) cell infiltrates. * P< 0.05, ** P< 0.01 and *** P< 0.001 as compared to control; + P< 0.05 shows a significant difference compared to the LPS group.

Discussion

In the present study, a single injection of LPS (5 mg/kg) in C57 mice induced a cascade of inflammatory processes in the lung tissue as demonstrated by elevated of NO, TNF-α and IL-1β levels. It is well documented that systemic injection of high-dose LPS can induce endotoxemia and sepsis-like symptoms in mice and rats (17, 21-23). ARDS and ALI are among the most severe and common consequences of sepsis, which might cause a high rate of mortality and morbidity (24). In addition to induction of systemic inflammation (25), LPS administration has been shown to increase lung tissue permeability and microvascular injury (26) which might be associated damage to alveolar structure, neutrophil and macrophage infiltration and induction of proinflammatory cytokine release (27). In patients with severe asthma, elevation of serum TNF-α was shown to be associated with the release of chemokines from the lung endothelium and neutrophil infiltration (28). The hyper-inflammatory response of sepsis is accompanied by elevation of ROS, and these factors are responsible for major organ failures and mortality or morbidity (29, 30). In this study, increases in lung tissue MDA level and decreases in CAT and SOD activity are in line with previous studies indicating oxidative stress elevation in sepsis (17, 30). Moreover, histopathological evaluation showed that LPS injection results in alveolar and interstitial neutrophil infiltration, edema, congestion, and accumulation of protein debris in lung tissue, and these destructive processes are associated with hyperactive oxidative stress and

inflammatory response**.** These results are in line with previous findings mentioning that the activated and primed leukocytes (neutrophils) are one of the main sources of ROS and inflammatory mediators that damage lung epithelium and endothelium of alveolar capillary (31).

It has been indicated that NMDARs play a vital role in the respiratory system normal function and subsequently, their over-excitation is related to pathogenesis of different respiratory conditions like COPD and asthma (32). One of the pivotal units in the mammalian biological system is xCT or x functional unit of the cystine system, which is upregulated in pulmonary system, and is mainly induced by lipopolysaccharides (33-35). It was reported that xCT pathway has a mediating role in glutamate increase by bleomycin in the pulmonary system (36). Another study revealed that glutamate release is increased in LPS-induced COPD in rats (11), which shows its role in respiratory disease inflammation.

In this study, memantine administration before and after induction of sepsis in a dose-dependent manner ameliorated LPS-triggered markers of ALI. Memantine 20 mg/kg decreased the lung tissue inflammatory markers (TNF-α and IL-1β), NO, and MDA levels, while increasing CAT activity. In a study, memantine injection lowered bleomycin-induced ALI and IL-1β elevation in rats (36). Another study that reports results consistent with ours, suggested that 25 mg/kg of memantine blocks LPS-induced TNF-α hyperproduction in COPD mice (11). In the present study, the highest dose of memantine (20 mg/kg) decreased the NO level. In agreement with our results, it has been reported that NMDA exposure led to increased NO levels in mice (37). The association of glutamate receptor activation and LPS-induced apoptotic and inflammatory responses has been indicated (38). Evidence on the role of NMDA agonists in ALI induction and elevation of glutamate release after LPS-mediated ALI might demonstrate the participation of NMDAR in lung injury (39, 40). Hu et al, suggested that memantine nitrate MN-80 exposure in rats ameliorated LPS-induced sepsis in ALI mice and suppressed immune system-induced pulmonary injury (41). Moreover, the involvement of NMDAR in the regulation of intracellular calcium, cytokines synthesis, and ROS production in immune cells (lymphocytes) has been shown (42, 43). Therefore, blockade of NMDAR could suppress glutamate-mediated effects of LPS in sepsis.

The protective effects of MK-801 (an NMDAR blocker) against LPS-induced ALI have been established as well. MK-801 had marked ameliorative effects against induction of the inflammation in airways and structural damage after tracheal LPS instillation. MK-801 treatment reversed oxidative stress elevation and suppressed inflammation and disarray in alveolar structure (31). It was proposed that the suppressive effects of MK-801 on allergy-induced lung inflammation might be through modifying pulmonary migration of immune cells and/or CNS-mediated endocrine signals to the periphery (corticosterone secretion) (43).

CAT is an important antioxidant enzyme. In the present study, the increase in CAT activity and decreases in NO and MDA levels observed in the animals treated with memantine 20 mg/kg might show the involvement of glutamate NMDAR in LPS-induced ALI. Histopathological evaluation also indicated that memantine (20 mg/kg) reduced neutrophil infiltration into the pulmonary alveolar cavity, interstitial space, and bronchiolar lumen, and lung congestion, which supports the biochemical results. Therefore, memantine at its highest dose could reduce inflammation- and oxidative stress-induced lung injury.

As a limitation, it should be noted that we were unable to investigate the mechanisms that contributed to the lung injury, for instance, TRL4/NF-kB signaling pathway or the expression of glutamate and NMDAR in the lung tissue, due to time and financial constraints. In addition, we could not determine the characteristics of bronchoalveolar lavage fluid because of the

limited lung tissue samples that could be harvested from mice; this point needs to be addressed in future studies.

A single intraperitoneal (i.p.) injection of LPS (5 mg/kg) induced oxidative stress, elevated inflammatory cytokine levels, and neutrophil infiltration into alveolar, which are the markers of lung injury. However, both pre- and post-treatment with memantine exerted protective and therapeutic effects against LPS-induced lung inflammation.

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Conflict of interest disclosure
There is no conflict of interest to be disclosed.

Ethics approval statement
All animal experimental procedures were done as per the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and they we reviewed and approved by the ethics committee of the Mashhad University of Medical Sciences (IR.MUMS.AEC.1402.021).

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Authors' Contributions
A.G. performed the experiments, carried out data analysis, and prepared the original draft. M.H. contributed to experimental conceptualization and participated in review and editing. M.H.B. provided supervision and reviewed the original draft. M.G. conducted the histopathological evaluation and contributed to review and editing. Z.G. contributed to conceptualization, methodology, validation, supervision, data analysis, writing, review, and editing. All authors read and approved the final version of the manuscript.

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