Am J Transl Res 2021;13(4):2563-2570
www.ajtr.org /ISSN:1943-8141/AJTR0125571

Original Article

Aerosol inhalation of edaravone can improve inflammation, oxidative stress and pulmonary function of rats with smoke inhalation injury by down-regulating miR-320

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Received November 4, 2020; Accepted December 4, 2020; Epub April 15, 2021; Published April 30, 2021

Abstract: Objective: To explore the protective effects and related mechanism of aerosol inhalation of edaravone on inflammation, oxidative stress and pulmonary function (PF) in rats with smoke inhalation injury. Methods: Twenty-four rats were stochastically and equally divided into four groups: group A (edaravone-preventing group), group B (model group), group C (low-dose group) and group D (high-dose group). The serum of rats was collected to determine the expression of miR-320, inflammatory mediators (TNF-α, IL-6, IL-10), oxidative stress indexes (MDA, SOD, MPO) and oxygenation index (OI). Pulmonary tissues of rats were collected to determine the total lung water (TLW), wet-to-dry ratio (W/D) and other parameters. HE staining was adopted for pathological evaluation. Results: Compared with group B, the levels of miR-320, TNF-α, IL-6, MDA, MPO, TLW and W/D in group A were significantly down-regulated, while IL-10, SOD and OI levels were significantly up-regulated, and the trend of this change was more obvious than that in group C and group D, with notably better improvement degree in group D than group C. In HE staining, the pulmonary tissue structure was basically normal in group A, and was better than that of the other three groups. In group B, the pulmonary tissue was seriously damaged, accompanied by a large number of inflammatory cells infiltration and alveolar wall thickening. The pathological condition of group C was notably ameliorated, the extent of this improvement was more pronounced in group D, and the degree of pathological improvement in group D was superior to that in group C. Conclusion: Aerosol inhalation of edaravone in advance can reduce the levels of inflammatory factors and oxidative stress indexes in serum of smoke inhalation injury rats, thus protecting PF, which may be related to the down-regulation of miR-320 by edaravone.

Keywords: Aerosol inhalation, edaravone, miR-320, smoke inhalation injury, pulmonary function

Introduction

Smoke inhalation injury is one of the main causes of death of burn patients, and the main causative factor of smoke inhalation injury is the hot air of smoke machines [1]. A study supported that the smoke contains not only hot carbon particles, but also complex chemical substances, which causes common damage to the respiratory tract of patients' pulmonary tissues [2]. The causes of smoke inhalation injury are extremely complex, with short courses of disease and rapid onset. As a result of hypoxia poisoning and other factors, secondary injury of other organs will occur, and then develop into a multiple organ dysfunction syndrome [3]. Although the current treatment for smoke inhalation injury has been improved, its mortality rate remains high [4].

Edaravone is considered as a free radical scavenger, which exists in the form of anions in the body and can scavenge free radicals by supplying one electron to them, thus inhibiting lipid peroxidation and reducing the destruction of nucleic acids and proteins to a certain extent [5]. Edaravone is lipolyphilic in the body and can penetrate the membrane of tissue cells and endothelial cells, so it can easily penetrate into various tissues, organs, arteries and veins of

the body [6]. When edaravone is used, its concentration will remain stable in the patient's tissues and blood vessels, thus exerting a good pharmacological effect [7]. It has been pointed out that some cytokines and inflammatory mediators play a certain part in pulmonary injury and systemic secondary injury. Hence, the pathway that mediates the release and clearance of these inflammatory factors may become a potential target for smoke inhalation injury treatment. MiR is a small non-coding RNA molecule that can be used as a potential biomarker for cancer diagnosis, personalized treatment and prognosis [8, 9]. MiR produces a marked effect on regulating the pathogenesis of smoke inhalation injury. In the research of Zhang et al. [10], miR-155, as a mediator of inflammatory reaction, participates in the pathogenesis of smoke inhalation pulmonary injury. Besides, it is suggested that smoke inhalation can lead to an increase in miR-155 expression, while inhibiting miR-155 can inhibit the inflammatory reaction of pulmonary injury caused by smoke inhalation. One study [11] supported that the imbalance of miR-320 is related to the pathogenesis of acute pulmonary injury, which is significantly up-regulated in acute pulmonary injury and positively correlated with the level of inflammatory factor TNF-α, suggesting that miR-320 is involved in the pathological mechanism of pulmonary injury.

At present, there are few studies on the regulatory mechanism of edaravone and miR-320 in smoke inhalation injury. Whether edaravone can play a protective part in smoke inhalation injury via mediating miR-320 remains to be confirmed.

Materials and methods

Animal origin

Twenty-four clean Sprague-Dawley (SD) rats aged 6-8 weeks were purchased from Experimental Animal Center of Zhejiang Academy of Medical Sciences (Hangzhou, China) and kept in a specific pathogen free environment with good ventilation. Before the experiment, all animals were housed for one week with an indoor humidity of 48-59% and a temperature of 21-26°C. The experiment was authorized by the hospital ethics committee, and the experimental process was in compliance with the Guideline for the Care and Use of Laboratory Animals [12].

Establishment and grouping of rat model of smoke inhalation injury

Twenty-four rats were randomly divided into group A (edaravone-preventing group), group B (model group), group C (low-dose group) and group D (high-dose group).

Modeling [13]: A self-made fully sheathed case with a double pulling plate was used, and white pine sawdust was placed as smoking material. The electric furnace was turned on and smoked for 15 min. Then, rats were anesthetized through intraperitoneal injection of 100 mg/kg ketamine, put into the smoke case and taken out after 5-minute smoking on their own. After an interval of 2 min, they were put into the case for smoking for another 5 min. White pine sawdust was not placed in group A, and other steps were the same.

Intervention: After successful modeling, the rats were placed in an indoor well-ventilated area for 30 min. When rats were conscious and breathed normally, rats in group A were given 0.5 mg/ml edaravone aerosol for 30 min before modeling, rats in group B were given equal dose of distilled water, rats in group C were given 0.5 mg/ml edaravone aerosol for 30 min, and rats in group D were given 1 mg/ml edaravone aerosol for 30 min. No rats died during modeling and intervention, and the rats were allowed to move freely within 6 hours after injury.

Outcome measures

(1) Detection of miR-320 expression using RT-PCR: the total RNA was extracted with Trizol kit (Wanlei Biotechnology Co., Ltd., Shenyang, China, WLA088b). Determination of purity, concentration and integrity of total RNA adopted ultraviolet spectrophotometer (Spectrometer Experimental Equipment Technology Co., Ltd., Donguan, China, UV1810S) and agarose gel electrophoresis (Yiji Industries Co., Ltd., Shanghai, China, S64967). RNA was reverse-transcribed into cDNA according to the instructions of the reverse transcription kit (Huada Protein Research and Development Center Co., Ltd., Beijing, China, BPI01030). SYBR Premix Ex Taq TM kit (Think-Far Technology Co.,

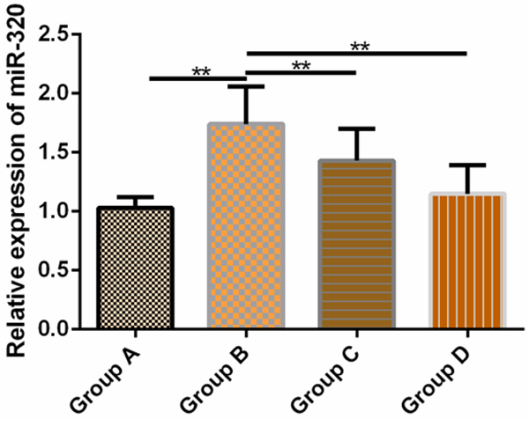

Figure 1. Effects of edaravone on miR-320 expression in serum of four groups of rats. Bar graph showing miR-320 relative expression in serum of four groups of rats. Note: Compared with group A or between two groups, *P < 0.05, **P < 0.01.

Ltd., Beijing, China, DRR420A) was applied. With U6 as internal reference, the reaction was performed on the PCR instrument. PCR amplification conditions were as below: first, pre-denaturation at 95°C for 10 min, then denaturation at 95°C for 15 s, and annealing/extension at 60°C for 60 s, with 40 cycles in total. The data were acquired after three repeated experiments, and the relative expression was calculated using $2^{-\Delta\Delta CT}$.

(2) Pulmonary function (PF) indexes: the PF indexes of the four groups of rats were determined by a lung function tester for small animals (Ranger Apparatus Co., Ltd., Shanghai, China, RZ-flexi), including peak expiratory flow (PEF), forced expiratory volume in the first second (FEV1) and FEV1/forced vital capacity (FVC).

(3) Detection of oxidative stress and inflammatory factors: 5 mL of femoral artery blood was extracted from four groups of rats, centrifuged (1500×g, 4°C, 10 min), and placed in a low temperature refrigerator at -70°C for later use. Enzyme-linked immunosorbent assay (ELISA) [14] was applied for the determination of the levels of malondialdehyde (MDA), superoxide dismutase (SOD), myeloperoxidase (MPO), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-10, which was conducted according to the instructions in the kits of MDA, SOD, MPO (Guang Rui Biological Technology Co., Ltd., Shanghai, China, elisa387, elisa388, elisa352), TNF-α, IL-6, and IL-10 (Shinuoda Biological Technology Co., Ltd., Chuzhou, China, SND-M198, SND-H1925, SND-H148).

(4) Oxygenation index (OI): the oxygenation index of four groups of rats was analyzed by Roche Cobasb blood gas analyzer (Kun Shilan Biotechnology Development Co., Ltd., Shanghai, China, cobas b 123).

(5) Measurement of total lung water (TLW) and wet/dry ratio (W/D): the rats were killed, and the pulmonary tissue samples of each group were collected. The left pulmonary tissue was weighed after being isolated, and wrapped in tin foil and placed in a constant temperature drying oven at 65°C for 72 h before measurement. The W/D and TLW were calculated.

(6) HE staining: the gross pathological changes of pulmonary tissue were observed. The right posterior lobe of lung was soaked in 4% neutral buffered formaldehyde solution (Solarbio, Beijing, China, DF0113), fixed for 24 h, and paraffin-embedded. It was consecutively sliced at 4 μm thickness for observation under a light microscope after routine HE staining.

Statistical methods

GraphPad 6 was applied for data analysis and image rendering. All the data were expressed in the form of mean ± standard deviation (mean ± SD). Comparison between two groups adopted independent sample t test. One-way analysis of variance (ANOVA) was utilized for intergroup comparison, represented by F. LSD-t test was applied for pair-wise comparison afterwards. Repeated measurement ANOVA was utilized for expression of multiple time points. Bonferroni was utilized for post hoc testing. When P < 0.05, significant difference was indicated. SPSS22.0 software was used for data analysis.

Results

Effects of edaravone on miR-320 expression in serum of four groups of rats

We detected the expression of miR-320 in the serum of the rats in each group and found that it was lower in serum of rats in group A. Besides, miR-320 in the serum of rats in group C and group D was lower when compared with group B (P < 0.05) (**Figure 1**).

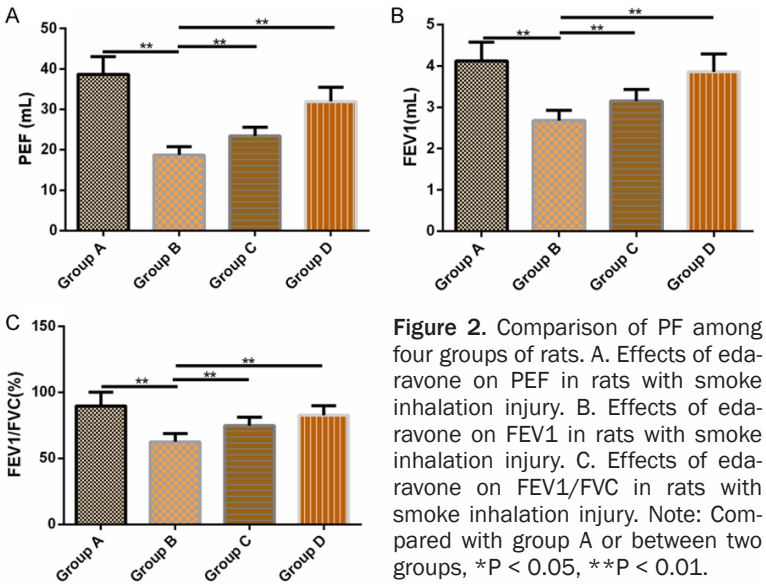

Figure 2. Comparison of PF among four groups of rats. A. Effects of edaravone on PEF in rats with smoke inhalation injury. B. Effects of edaravone on FEV1 in rats with smoke inhalation injury. C. Effects of edaravone on FEV1/FVC in rats with smoke inhalation injury. Note: Compared with group A or between two groups, *P < 0.05, **P < 0.01.

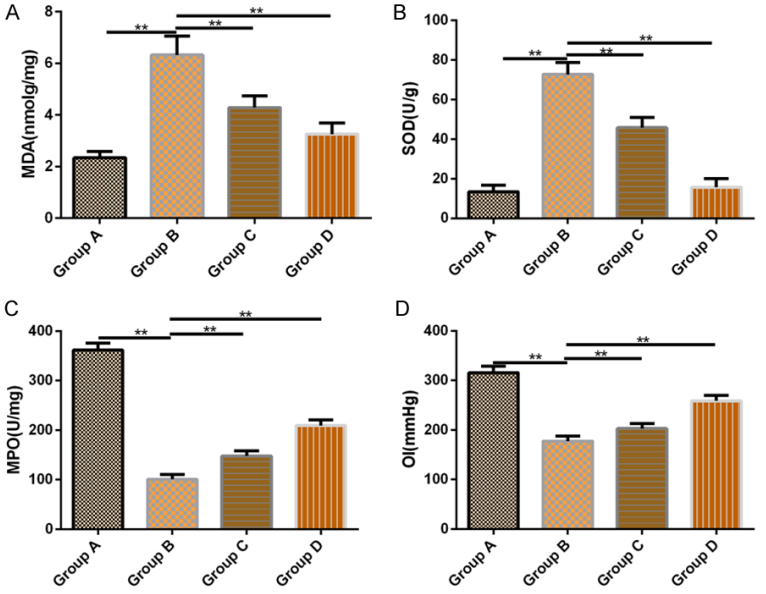

Figure 3. Effects of edaravone on serum oxidative stress indexes and oxygenation index in rats with smoke inhalation injury. A. Effects of edaravone on MDA concentration in rats with smoke inhalation injury. B. Effects of edaravone on SOD concentration in rats with smoke inhalation injury. C. Effects of edaravone on MPO concentration in rats with smoke inhalation injury. D. Effects of edaravone on OI concentration in rats with smoke inhalation injury. Note: Compared with the control group or between two groups, *P < 0.05, **P < 0.01.

Comparison of PF among four groups of rats

Compared with group A, the indexes of PEF, FEV1 and FEV1/FVC in group B decreased notably (P < 0.05), while the indexes of PEF, FEV1 and FEV1/FVC in group C and group D increased notably when compared with group B (P < 0.05) (**Figure 2**).

Effects of edaravone on serum oxidative stress indexes and oxygenation index in rats with smoke inhalation injury

We examined the impacts of edaravone on serum oxidative stress indexes and oxygenation index of four groups of rats. The results showed that compared with group A, MDA and SOD levels in group B increased remarkably, while MPO and OI levels decreased remarkably (P < 0.05). Compared with group B, the expression levels of MDA and SOD in rats in group C and Group D were remarkably decreased, while the levels of MPO and OI were remarkably increased (P < 0.05), with statistically significant differences (P < 0.05) (**Figure 3**).

Comparison of W/D and TLW in rats of the four groups

We examined PF indexes in the four groups. Compared with group A, the W/D and TLW of rats in group B elevated significantly (P < 0.05), while those of group C and group D decreased significantly when compared with group B (P < 0.05). The difference was statistically significant (P < 0.05) (**Figure 4**).

Effects of edaravone on serum inflammatory factors in rats with smoke inhalation injury

Compared with group A, TNF-α and IL-6 levels in the serum of rats in group B increased notably, while the expression of IL-10 decreased notably (P < 0.05). Compared with group B, TNF-α and IL-6 expression of rats in group C and group D decreased notably, while IL-10

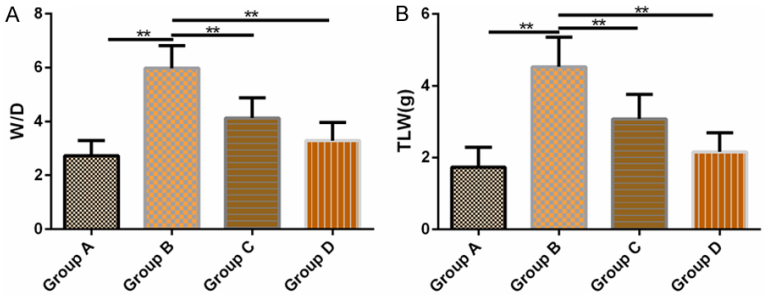

Figure 4. Comparison of W/D and TLW in rats of the four groups. A. Effects of edaravone on W/D in rats with smoke inhalation injury. B. Effects of edaravone on TLW in rats with smoke inhalation injury. Note: Compared with the control group or between two groups, *P < 0.05, **P < 0.01.

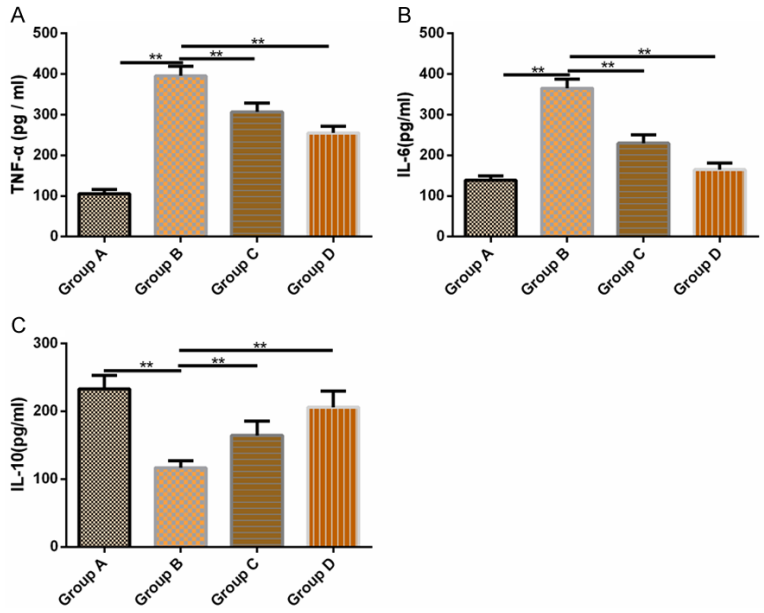

Figure 5. Effects of edaravone on serum inflammatory factors in rats with smoke inhalation injury. A. Effects of edaravone on TNF-α concentration in rats with smoke inhalation injury. B. Effects of edaravone on IL-6 concentration in rats with smoke inhalation injury. C. Effects of edaravone on IL-10 concentration in rats with smoke inhalation injury. Note: Compared with the control group or between two groups, *P < 0.05, **P < 0.01.

increased notably, with statistically significant differences (P<0.05) (**Figure 5**).

Pulmonary histopathological examination results of four groups of rats

We observed the pulmonary tissue of the four groups of rats after HE staining. Rat pulmonary tissue structure in Group A was basically normal, the alveoli were intact, the intervals were uniform, and there was no exudate or infiltration of red and white blood cells in the cavity. In group B, the pulmonary tissue was wet with ecchymosis, the alveolar structure was destroyed, the interval was extremely uneven, there was a large number of neutrophils infiltrated, and the alveolar wall was hyperemic and thickened. In group C, the congestion and edema of pulmonary tissue were alleviated, the size and shape of alveoli were still irregular, the infiltration degree of white blood cells in alveolar septum was reduced, and the alveolar septum was slightly even. In group D, the congestion and edema of pulmonary tissue were obviously alleviated, the alveolar structure was relatively clear, and a few red and white blood cells were found in the alveolar cavity, which was less severe than that in group C. See **Figure 6**.

Discussion

Smoke inhalation injury is a serious burn disease which develops rapidly, and its mechanism is complex [15]. The level of pro-inflammatory cytokines in patients with smoke inhalation injury increases with time, but the mechanisms in the regulation of inflammatory mediators have not been effectively solved [16]. Edaravone is a free radical scavenger, which has anti-apoptosis, necrosis and anti-inflammatory effects, and has protective effects on heart, brain and lung in cardiovascular diseases and acute pulmonary injury [17]. However, the mechanism is not fully clarified, which is also the reason why this experiment is designed. We found through this study that edaravone can exert pulmonary protection by regulating miR-320.

A previous study showed that [18] smoke inhalation injury can lead to inflammatory exudate in pulmonary tissue of patients, accompanied by significant edema. With the extension of time, it will also lead to thickening of alveolar septum and collapse of alveoli, which will cause

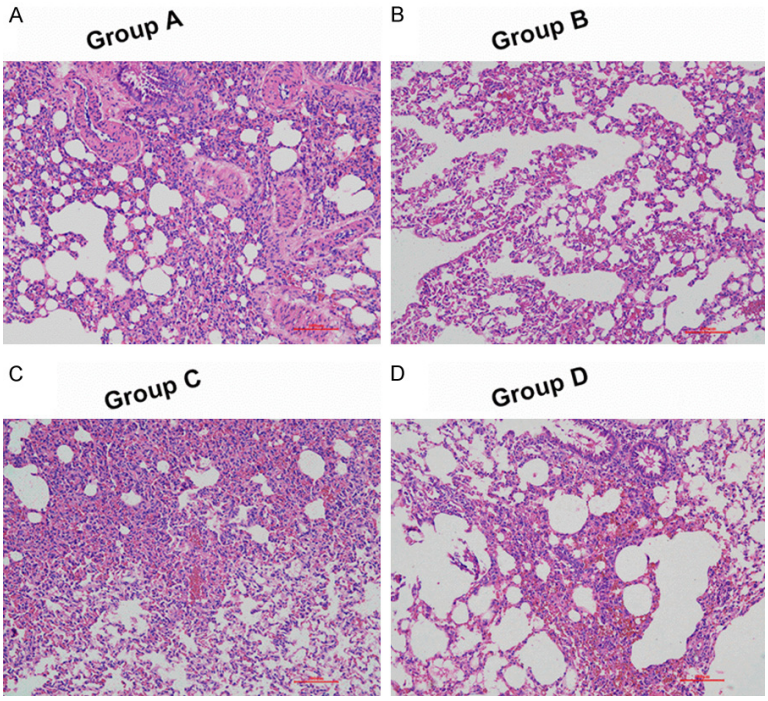

Figure 6. Lung histopathological examination results of four groups of rats. A. HE staining picture of pulmonary tissue of rats in group A. B. HE staining picture of pulmonary tissue of rats in group B. C. HE staining picture of pulmonary tissue of rats in group C. D. HE staining picture of pulmonary tissue of rats in group D.

serious damage to PF. It can also give rise to inflammatory reaction in patients' lungs or decrease of oxygenation index [19]. Edaravone can significantly improve the PF. For example, in the rat model of acute pancreatitis with impaired PF, the intervention of edaravone can reduce the levels of inflammatory factors in the lung, and protect rat from pulmonary injury through antioxidant and anti-inflammatory effects [20]. Here, the indexes of PEF, FEV1 and FEV1/FVC decreased considerably after smoke inhalation injury, while the improvement of PF indexes of rats receiving edaravone in advance was notably better than that of rats in group C and D, indicating that edaravone intervention in advance can better improve PF. Research showed that pulmonary injury caused by smoke inhalation can trigger inflammatory cascade reaction. Meanwhile, it greatly increases active oxygen and active nitrogen in lung, which leads to oxidative stress. Besides, the enhancement of oxidative stress is an important cause of pulmonary injury [21]. As indicated in the study of Ke et al. [22], edaravone can reduce apoptosis and oxidative stress in intestinal mucosal barrier dysfunction patients after burn via regulating the expression of miR-320, which is similar to the results of this study. In this experiment, after smoke inhalation injury, MDA and SOD levels increased notably and MPO and OI levels decreased notably in rats, while the oxidative stress indexes of rats receiving edaravone inhalation in advance were notably improved, and the improvement degree was significantly superior to that in group C and group D. The above results indicated that edaravone plays a vital part in the antioxidation of rats with smoke inhalation injury, and edaravone inhalation in advance is associated with greater improvement.

A previous study [23] found that the W/D is significantly increased in smoke inhalation injury model, which is similar to this study. According to this study, the W/D and TLW of rats with smoke inhalation injury elevated notably, while the two of rats with smoke inhalation injury decreased notably after the intervention with edaravone. The above result suggested that edaravone intervention can gradually reduce the W/D of rats with smoke inhalation injury, which can considerably alleviate the degree of pulmonary tissue injury in rats. Besides, edaravone inhalation given in advance can better improve the lung tissue of rats. Smoke inhalation injury causes inflammation in the body and increases capillary permeability in the lungs, which exacerbates the severity of pulmonary edema. TNF-α and IL-6 are crucial in smoke inhalation injury [24, 25], indicating that increased levels of inflammation damage the lungs. The study of Bao et al. demonstrated that, in mice with pulmonary oxygen toxicity [26], edaravone treatment can reduce lung permeability of the mice and reduce the expression levels of pro-apoptotic proteins and inflammatory factors in the tissues, which finding is similar to ours. Here, the expressions of TNF-α, IL-6 and IL-10 in serum of four groups of rats were detected to indirectly reflect the degree of inflammatory

injury of lung. TNF-α and IL-6 expression in serum of rats after smoke inhalation injury elevated remarkably, while IL-10 expression reduced notably. Rats received edaravone inhalation in advance had notably improved inflammatory factor indexes, and the improvement was remarkably higher than that of group C and group D. The above result indicates that the intervention of edaravone can improve rat pulmonary tissues, reduce the release of inflammatory factors in rats' lungs, thus reducing the level of inflammatory factors *in vivo* and protecting the lungs, and inhalation in advance is associated with better efficacy. Finally, we observed the improvement of pulmonary tissue of four groups of rats through HE staining. The results showed that rat pulmonary tissue with smoke inhalation injury was seriously damaged, while the degree of rat pulmonary tissue injury with smoke inhalation injury was significantly improved after the intervention of edaravone, indicating that edaravone intervention can effectively ameliorate the degree of pulmonary injury and protect the lung, and edaracone inhalation in advance can reduce pulmonary tissue damage in rats to a greater extent. According to our study, edaravone can effectively reduce the level of miR-320 in serum of rats with smoke inhalation injury in vivo, and injecting miR-320 inhibitor into the rat model of smoke inhalation injury can play a similar therapeutic role as edaravone. This suggested that edaravone can take effect in treating smoke inhalation injury rats through regulating the expression of miR-320.

To sum up, aerosol inhalation of edaravone in advance can reduce the levels of inflammatory factors and oxidative stress indexes in the serum of smoke inhalation injury rats, thus protecting PF, which may be related to the down-regulation of miR-320 expression by edaravone. However, there is still room for improvement. For example, whether there is a dose-dependent relationship between the regulation mechanism of edaravone in rats with smoke inhalation injury should be investigated. We will gradually improve the study from the above perspective in the future.

Acknowledgements

This study is financially supported by Chengde science technology research and development plan project (201904A107).

Disclosure of conflict of interest

None.

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