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Retrospective study of clinical features and prognosis of edaravone in the treatment of paraquat poisoning

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Abstract

To observe whether edaravone can protect organs and inhibit pulmonary fibrosis in patients with paraquat poisoning and to provide a method for clinical intervention for paraquat poisoning.

Forty-four cases of paraquat poisoning were collected from March 2011 to December 2017 in our hospital. Eighteen cases from March 2011 to November 2013 did not receive edaravone treatment and were considered the control group, and 26 cases from January 2014 to December 2017 were treated with edaravone and were considered the observation group. Injuries to the central nervous system, heart, liver, kidney, and digestive system were evaluated on at 24 hours, 3 days, and 7 days after hospitalization. The expression of serum inflammatory factors (interleukin [IL]-6, IL-10, tumor necrosis factor-α [TNF-α]) and oxidative stress correlation (superoxide dismutase [SOD] and malondialdehyde [MDA]) were assayed at 24 hours, 3 days, and 7 days after being hospitalized. After 7, 14, and 30 days, the changes in pathological lung characteristics in the 2 groups were assessed, and survival rates were calculated.

Edaravone significantly increased the serum levels of SOD and obviously markedly reduce the serum levels of IL-6, IL-10, TNF-α, and MDA in patients poisoned with paraquat ($P < .05$). Edaravone significantly protected the liver ($P = .021$), cardiovascular ($P = .031$), and renal ($P = .028$) organs of patients from paraquat poisoning-induced injury after 7 days but had no significant protection or improvement on respiratory and digestive tract damage. Edaravone delayed the occurrence of pulmonary fibrosis and increase the survival time of patients at 7 and 14 days ($P < .05$). However, the 1-month follow-up found that edaravone did not reduce pulmonary fibrosis (77.8% vs 73.1%, $P = .615$) and did not increase the survival rate of the patients (61.1% vs 65.3%, $P = .853$).

Edaravone is beneficial for protecting the kidneys and liver from paraquat poisoning through reducing oxidative stress and inhibiting inflammatory response. It can also inhibit the pulmonary fibrosis process and prolong the survival time of the patients. However, no significant improvements were seen in the probability of pulmonary fibrosis and the survival rate.

Abbreviations: CT = computed tomography, ELISA = enzyme-linked immunosorbent assay, IL-10 = interleukin 10, IL-6 = interleukin 6, MDA = malondialdehyde, PQ = paraquat, SOD = superoxide dismutase, TNF-α = tumor necrosis factor-α.

Keywords: edaravone, inflammation, oxidative stress, paraquat poisoning, pulmonary fibrosis

1. Introduction

Paraquat (PQ) is widely used as a pyridine herbicide. It can be absorbed by the skin and respiratory tract and is strongly toxic to humans and animals.[1] PQ has a low lethal dose and no effective antidote. There is no specific drug to treat PQ poisoning, and the mortality of PQ poisoning patients is still high.[1,2] Therefore, finding an effective treatment to improve the prognosis of PQ poisoning is attracting the attention of the hospital and the community.

The lungs are the main target organs of PQ, which results in major pathological manifestations of acute alveolar epithelial cytotoxicity during PQ poisoning. It is thought that PQ can cause a redox reaction, resulting in cell injury and persistent inflammation.[3,4] Edaravone is a free radical scavenging drug, and it has antiapoptotic, necrotic, and anti-inflammatory effects. This drug shows protective effects on the heart, lungs, and brain in cardiovascular disease and acute lung injury.[5,6] Animal experiments have shown that edaravone could inhibit PQ induced lung injury and fibrosis in rats.[5–7] Therefore, 58 PQ poisoning cases treated in our hospital were retrospectively analyzed to observe whether edaravone could protect organs and inhibit pulmonary fibrosis. This analysis may provide a

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The authors declare that there is no duality of interest associated with this manuscript.

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theoretical basis and a method for clinical intervention in cases of PQ poisoning.

2. Methods and clinical data

2.1. Clinical data collection

Forty-four cases of oral PQ poisoning were collected from March 2011 to December 2017 in our hospital. Eighteen cases from March 2011 to November 2013 did not receive edaravone treatment and were considered the control group; 26 cases from January 2014 to December 2017, were treated with edaravone and were considered the observation group. The inclusion criteria were as follows: ① the patient poisoned within 4 to 8 hours from the rescue time, ② intoxication by oral 20% PQ, ③ no other drug poisoning, ④ no other previous serious illness, ⑤ the age distribution of the enrolled patients enrolled was 25 to 50 years. The exclusion criteria were as follows: ① patients with other pulmonary diseases, ② patients with other serious diseases or medical history of organ dysfunction, ③ pregnant, lactating, or mentally ill women, ④ Combination of other drug poisoning, ⑤ patients died or were discharged from hospital within 24 hours, ⑥ men with mental illness. The clinical data of 2 groups of patients were collected. This study was approved by the ethics committee of Jinling Hospital, Medical School of Nanjing University (2017-0011). All patients signed informed consent.

2.2. Treatment measures

After being hospitalized, 2 groups of patients were given conventional treatment as follows: adequate gastric lavage, catharsis, fluid replacement, correction of electrolyte disorders, acidosis, organ protection, and other symptomatic treatments. Then, 30% bleached soil was used to fill the stomach. Patients' stool was collected. Blood perfusion was strengthened twice each day and lasted for 5 days. Intravenous infusion of hormones and immunosuppressants, ambroxol hydrochloride injection, vitamin C, vitamin E, and glutathione injection were carried out. The observation group was given 30 mg edaravone on the basis of routine treatment and intravenously injected with 250 mL saline, twice a day, for a total of 7 to 14 days.[7] In addition to the edaravone treatment, both groups received the same care according to standard procedures.

2.3. Detection of inflammation and antioxidants by enzyme-linked immunosorbent assay

Two groups of patients' serum samples were collected at 24 h, 3 days, and 7 days after being hospitalized. Enzyme-linked immunosorbent assay (ELISA) was used to detect the expression of serum inflammatory factors (interleukin [IL]-6, IL-10, tumor necrosis factor-α [TNF-α]) and antioxidant superoxide dismutase (SOD2). A thiobarbituric acid colorimetric assay was used to detect the expression of the serum antioxidant the results can be read in the medical record system.

2.4. Evaluation of organ function

Arterial blood gas analysis, plasma PQ concentration, myocardial enzymes, and liver and kidney function were detected by automatic biochemical analyzer. The hospital clinical laboratory assisted in these assays, and the results can be read in the medical record system. The changes of nerve, heart, liver, kidney, and digestive systems in 2 groups of patients were evaluated and recorded at 24 hours, 3 days, and 7 days after being hospitalized. Clinical evaluation of data collection standards were as follows: ① neurological complications: disturbance of consciousness or convulsion; ② liver injury: alanine aminotransferase and aspartate aminotransferase higher than 60 U/L; ③ renal injury: serum creatinine higher than 1. 4 mg/dL; ④ respiratory failure: arterial oxygen partial pressure less than 60 mm Hg, partial pressure of carbon dioxide less than 50 mm Hg, or respirator assisted breathing needed; ⑤ cardiovascular complications: CK-MB greater than 25 U/L, hypotension, arrhythmia, shock, and so on; ⑥ digestive tract injury: the presence of hematemesis and lack stool. After 7, 14, and 30 days, the changes of lung characteristics in the 2 groups were collected and the survival rates were calculated. The changes in lung characteristics were determined through computed tomography (CT). CT results were evaluated by experienced radiologists. Pulmonary CT examinations showed mesh shadow, irregular thickening of interlobular septa, and pulmonary consolidation was the main feature of pulmonary fibrosis.

2.5. Statistical analysis

Statistical analysis was performed with SPSS 22.0. The measurement data were expressed as the mean ± standard deviation (X ± S), number and percentage of cases. One-way ANOVA was used to assess treatment-induced differences between groups. Pulmonary fibrosis and gender differences between the 2 groups were analyzed by χ^2 test, and the alpha level was set to 0.05, with $P < .05$ considered a statistically significant difference.

3. Result

3.1. Characteristics of the patients included in the study

A total of 44 patients with PQ poisoning who were brought to our hospital from March 2011 to December 2017 were included in the study. As shown in Table 1, there was no significant difference in gender, age, temperature, heart rate, respiratory frequency, mean arterial blood pressure, blood pH, plasma PQ concentration, time of poisoning, severity index score of PQ poisoning, and Glasgow coma score between the 2 groups.

3.2. Edaravone treatment significantly decreases the expression of IL-6, IL-10, and TNF-α in serum of patients at 24 hours, 3 days, and 7 days after being hospitalized

The results of ELISA test showed that the serum levels of IL-6, IL-10, and TNF-α in 2 groups of patients were higher at 24 hours, but there was no significant difference between the 2

Table 1

Characteristics of the 2 groups of patients in the study.

Parameter	Control group (n = 18)	Observation group (n = 26)	P
Sex (male/female)	6/12	12/14	.725
Age (age)	35.57 ± 6.12	37.17 ± 5.75	.617
Temperature, °C	36.12 ± 0.45	36.52 ± 0.52	.274
Heart rate, times/min	81.62 ± 6.35	84.12 ± 7.52	.674
Respiratory frequency, times/min	23.22 ± 4.35	22.22 ± 6.35	.459
Mean arterial blood pressure, mm Hg	87.62 ± 6.75	83.12 ± 8.52	.828
Blood pH	7.42 ± 0.62	7.38 ± 0.57	.426
Plasma PQ concentration, g/mL	0.82 ± 3.62	1.21 ± 2.85	.614
Time of poisoning, h	4.85 ± 3.14	5.01 ± 2.78	.241
Severity index score of PQ poisoning	4.52 ± 6.44	5.12 ± 5.91	.108
Glasgow coma score	14.32 ± 1.54	13.73 ± 1.75	.178

PQ = paraquat.

$P < .05$ means statistically significant.

groups (Fig. 1). Compared with the control group, the serum levels of IL-6, IL-10, and TNF-α in the observation group decreased significantly on the third and seventh days after being hospitalized. These results suggest that edaravone could reduce the IL-6, IL-10, and TNF-α levels induced by PQ (Fig. 1).

3.3. Expression of malondialdehyde and SOD2 in serum of patients with 24 hours, 3 days, and 7 days after being hospitalized.

Thiobarbituric acid colorimetric assay results showed that the serum content of malondialdehyde (MDA) in the 2 groups of patients was higher at 24 hours, but there was no significant difference between the 2 groups (Fig. 2). Compared with the control group, the serum MDA levels of the observation group were significantly decreased on the third and seventh days after being hospitalized. ELISA results showed that the levels of SOD serum in the 2 groups did not increase, and there was no significant difference between the 2 groups. Compared with the control group, the serum SOD level of the observation group was significantly increased on the third and seventh days after being hospitalized.

3.4. Organ protection properties of edaravone in patients with PQ poisoning

As shown in Tables 2 to 4, the 2 groups of patients with neurological complications, cardiovascular system complications, digestive system complications, respiratory failure, liver, and kidney function injury were not significantly different at 24 hours and on the third day. The results on the seventh day showed that edaravone significantly protected the liver, cardiovascular, and kidneys of patients with PQ poisoning but had no significant protection or improvement on respiratory and digestive tract damage (Fig. 3).

3.5. Effect of edaravone on pulmonary fibrosis and survival rate in patients with PQ poisoning

All deaths occurred due to overdoses of PQ, complicated with respiratory failure and pulmonary fibrosis. This study showed that edaravone could delay the occurrence of pulmonary fibrosis and increase the survival time of patients at 7 and 14 days after poisoning. However, the 1-month follow-up found that edaravone did not reduce pulmonary fibrosis and did not increase the survival rate of the patients.

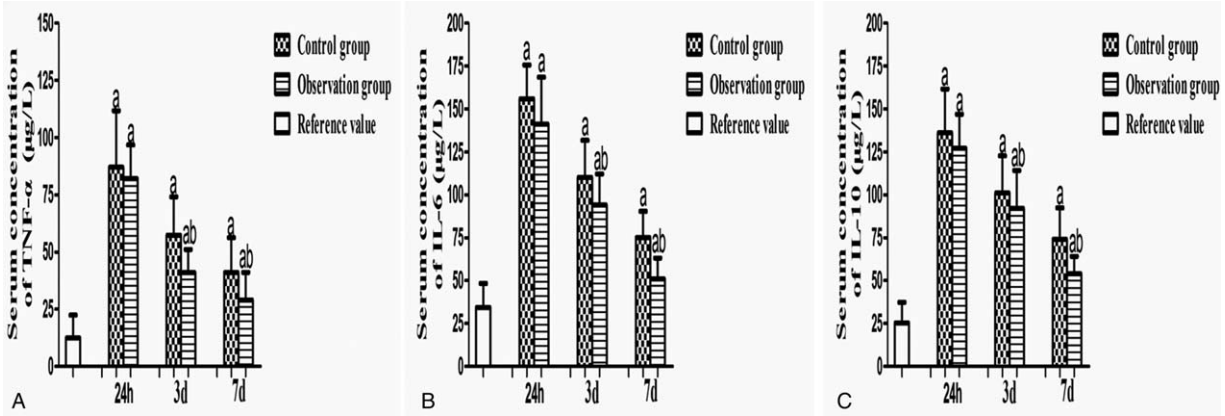

Figure 1. Serum levels of IL-6, IL-10, and TNF-α in 2 groups were detected by ELISA. ELISA = enzyme-linked immunosorbent assay, IL = interleukin, TNF-α = tumor necrosis factor α.

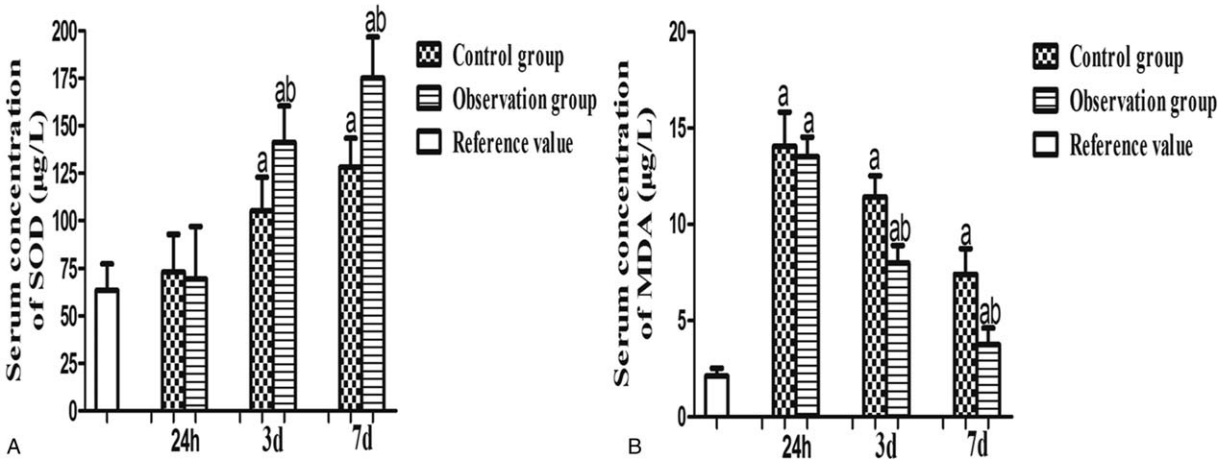

Figure 2. Serum levels of MAD and SOD2 in 2 groups. MAD = malondialdehyde, SOD2 = superoxide dismutase.

Table 2

The whole organ injury within 24 h.

Organ function	Control group (n = 18)	Observation group (n = 26)	χ^2	*P*
Nervous system	0	0	0	1.000
Cardiovascular system	3	5	0.305	.795
Digestive system	4	6	0.157	.615
Liver function injury	3	5	0.123	.702
Kidney function injury	3	4	0.375	.415
Respiratory failure	8	11	0.093	.915

$P < .05$ means statistically significant.

Table 3

The whole organ damage within 3 d.

Organ function	Control group (n = 18)	Observation group (n = 26)	χ^2	*P*
Nervous system	1	3	0.845	.370
Cardiovascular system	4	6	0.345	.628
Digestive system	6	9	0.657	.521
Liver function injury	6	8	0.523	.452
Kidney function injury	8	10	0.575	.483
Respiratory failure	11	17	0.493	.395

$P < .05$ means statistically significant.

Table 4

The whole organ damage within 7 d.

Organ function	Control group (n = 18)	Observation group (n = 26)	χ^2	*P*
Nervous system	2	3	0.745	.285
Cardiovascular system	8	4	5.345	.031
Digestive system	7	9	0.557	.412
Liver function injury	13	8	5.413	.021
Kidney function injury	12	8	5.073	.028
Respiratory failure	12	14	1.493	.265

$P < .05$ means statistically significant.

4. Discussion

PQ is a widely used, also known as herbicide, is a nonselective, fast acting herbicide. Patients with large doses of PQ died in the short term due to acute lung injury, liver failure, and kidney failure.[8] The main target organs of PQ injury are the lungs. The pathological changes follow this sequence: alveolar type I, type II epithelial cells were destroyed, a large number of neutrophils infiltrated the alveolar septum to form pneumonia, the normal alveolar structure was destroyed, resulting in gas exchange barriers, and the patients died early due to intractable hypoxemia.[9,10] Currently, the research on the mechanism of multiple organ dysfunction caused by PQ poisoning is mainly involved in calcium overload, inflammation overexpression, free radical and abnormal gene expression, in which excessive inflammatory reactions and oxidative stress are particularly important.[11–14] Animal and clinical studies have confirmed that PQ can promote the expression and release of NF-κB, IL-6, and TNF-α and thus cause damage to the lungs.[14,15] Additionally, PQ produces large amounts of oxidative free radicals, induces lipid peroxides, and directly damages the lungs and other tissues and organs. Edaravone was originally developed as a neuroprotective drug. It is a powerful antioxidant that has a very strong free radical scavenging ability and can reduce inflammatory factors including IL-6, TGF-β, and TNF-α.[16,17] This study found that PQ can induce the upregulation of IL-6, IL-10, and TNF-α in patients with PQ poisoning, but edaravone can inhibit the upregulation of these inflammatory factors (IL-6, IL-10, and TNF-α), which shows that edaravone has a good anti-inflammatory effect in the treatment of PQ poisoning (Table 5).

PQ poisoning can lead to a significant increase in reactive oxygen species, which has been identified as one of the important causes of acute tubular necrosis and acute kidney injury. Approximately 51% of intoxication patients will suffer from acute kidney injury and approximately 37% of patients will eventually die of renal failure or multiple organ failure.[18–20] Except for mild PQ poisoning, the most serious injury to the respiratory system, liver, and kidneys is caused by inhalation or intake of PQ from the digestive tract. Additionally, the main cause of death is the damage and failure of the cardiovascular system and other multiple systems in the middle and severe late stages of PQ poisoning.[18–20] At present, a large number of

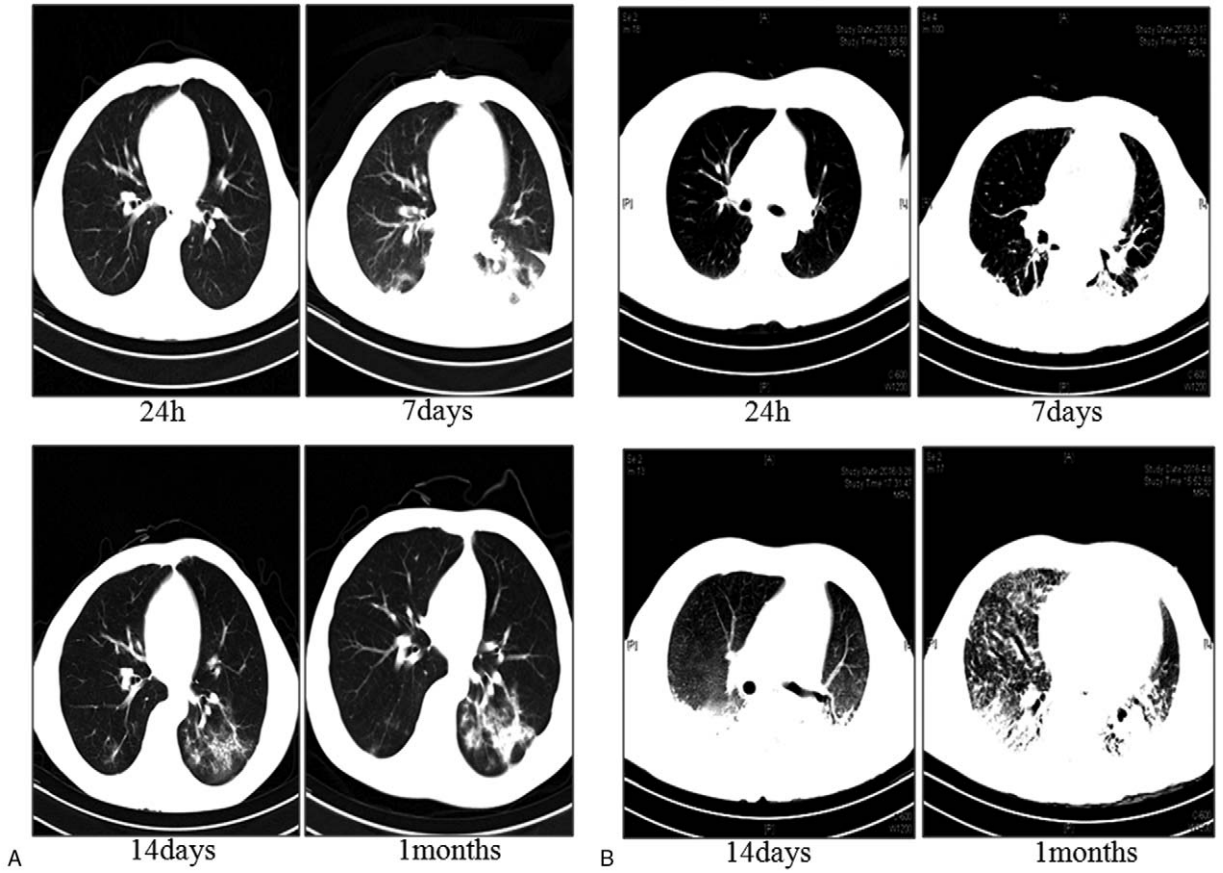

Figure 3. Representative CT photomicrograph showing changes in dynamic inflammation and fibrosis in the lungs of the 2 groups. A: Observation group, B: control group. Compared with the observation group, the lung fibrosis in the control group was serious. CT = computed tomography.

studies have confirmed that the changes in the levels of MDA and SOD reflect the ability of anti-lipid peroxidation and scavenging oxygen free radicals.[21,22] In this study, we found that edaravone could significantly inhibit the serum MDA content in patients with PQ poisoning, and increase the content of serum SOD. All of these revealed severe anti-lipid peroxidation damage and the ability to scavenge oxygen free radicals. In addition, this study showed that edaravone could significantly inhibit liver and kidney injury and cardiovascular complications in the middle and later stages of PQ poisoning. The possible reason is that edaravone is a new type of free radical scavenger, which inhibits the formation of free radicals and the lipid peroxidation chain reaction of the cell membrane, and effectively inhibits the destruction of proteins and nucleic acids. At the same time, a highly permeable edaravone can effectively inhibit the damage in tissue cells and the vascular endothelium, minimizing injury to tissues and preserving organ function. This allows it to function in protecting organs.

Lung injury is the most important consequence of PQ poisoning, because the alveolar type II cells have the characteristics of active uptake and accumulation of PQ, therefore the lung damage is the most obvious and serious sign of PQ poisoning.

Table 5

Comparison of CT lung characteristics and survival rate between 2 groups after seventh days' treatment.

		Pulmonary fibrosis		Without pulmonary fibrosis							
Time	Group	Death	Grid shadow	Grinding glass shadow	Recovery	Percentage of pulmonary fibrosis (%)	χ^2	*P*	Fatality rate (%)	χ^2	*P*
7 d	Control group (n=18)	4	7	6	1	61.1%	4.278	.014	22.2%	0.009	.686
	Observation group (n=26)	6	4	15	1	38.%			23.1%		
14 d	Control group (n=18)	9	4	2	3	72.1%	5.356	.027	50.0%	4.128	.031
	Observation group (n=26)	8	7	7	4	53.8%			30.7%		
1 mo	Control group (n=18)	11	3	2	2	77.8%	0.652	.615	61.1%	0.247	.853
	Observation group (n=26)	17	2	4	2	73.1%			65.3%		

$P < .05$ means statistically significant.

Lung injury is characterized by acute chemical pulmonary interstitial lesions and the rapid development of pulmonary fibrosis, resulting in intractable hypoxemia and respiratory failure, which eventually leads to multiple organ damage or failure.[9,19] Currently, there is no specific method for clinical treatment of PQ poisoning. It is mainly treated through gastric lavage, catharsis, hemoperfusion, hemodialysis clearance of poisons, steroid impact therapy against organ damage and symptomatic support therapy, and so on. However, the effect is not satisfactory, and thus, the mortality of PQ poisoning is very high, up to 50% to 80%.[1,23] Most studies have shown that edaravone can inhibit pulmonary fibrosis in animal experiments.[24,25] However, our results suggest that edaravone can delay pulmonary fibrosis, but does not inhibit the development of pulmonary fibrosis. Edaravone significantly delayed pulmonary fibrosis and increased the patients' survival time at seventh and fourteenth days of treatment, but at the 1-month follow-up, edaravone did not reduce the incidence of pulmonary fibrosis or increase the patients' survival rate. Edaravone can delay the production and development of pulmonary fibrosis, increase the survival time of the patients, and provide a possible follow-up treatment, but does not reverse the development of pulmonary fibrosis.

In conclusion, we found that edaravone had a strong protective effect on liver and kidney damage but had no significant improvement in the digestive tract and on the respiratory damage induced by PQ poisoning. Edaravone did not reduce pulmonary fibrosis in patients with PQ poisoning but did delay the generation and development of pulmonary fibrosis. Edaravone prolonged the survival time of patients, but had no significant effect on the survival rate. Certainly, because of the lack of sample size in this study, the design is not a multicenter randomized controlled study, more clinical and basic experimental studies are needed to further confirm our findings.

Author contributions

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Visualization: Ren Yi, Zhang Wei, Nie Shinan.
Writing – original draft: Ren Yi, Sun Zhaorui, Nie Shinan.
Writing – review and editing: Ren Yi, Nie Shinan.

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