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Original Article

Inhibitory effect of pirfenidone on pulmonary fibrosis in patients with acute paraquat poisoning

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Abstract: Objective: To study the efficacy of pirfenidone (PFD) on patients with pulmonary fibrosis caused by acute paraquat (PQ) poisoning. Methods: A total of 86 patients with pulmonary fibrosis caused by acute PQ poisoning admitted to our hospital were analyzed retrospectively. All of them successfully received the standard 21-day treatment based on "Taishan Consensus", and they were assigned to the PFD group or the NO-PFD group according to whether they received PFD treatment (at 200 mg/time, 3 times/day) for 6 months after discharge. The two groups were compared in effective treatment rate, mortality and incidence of adverse reactions such as liver and kidney function damage, pulmonary fibrosis-associated indexes, pulmonary function-associated indexes, and arterial blood gas indexes before and after therapy. Results: The PFD group showed a notably higher effective treatment rate than the NO-PFD group (P<0.05). Additionally, the PFD group showed notably lower levels of serum hyaluronic acid (HA), laminin (LN), type IV collagen (CIV), and type III procollagen (PCIII), and notably higher levels of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC than the NO-PFD group (all P<0.001), and the PFD group also showed significantly higher levels of arterial blood gas indexes including arterial partial pressure of oxygen (PaO_2) and PaO_2/inspired oxygen (FIO_2) than the NO-PFD group (both P<0.001). Moreover, the Kaplan-Meier survival curves showed that the survival rate of the patients in PFD group was significantly higher than that in the NO-PFD group (P<0.05). Conclusion: With a high safety, PFD can effectively improve the treatment efficacy in patients with pulmonary fibrosis caused by acute PQ poisoning. PFD can improve the pulmonary function and arterial blood gas status of patients, without causing obvious liver and kidney damage.

Keywords: Pirfenidone, hemoperfusion, hemodialysis, acute paraquat poisoning, pulmonary fibrosis, liver and kidney function

Introduction

Paraquat (PQ) is an effective non-selective contact organic nitrogen heterocyclic herbicide, with advantages of quick response, water resistance, no pollution, little residue, and strong herbicidal performance. It can be degraded by natural light, ultraviolet rays and soil microorganisms, and its degradation products are low in toxicity or harmless, so it has been widely applied in agricultural production in China. However, PQ is highly toxic to human and animals. It can be absorbed through the digestive tract, respiratory tract and even direct skin contact. A small amount of PQ can result in a terribly high mortality, and simply 20-40 mg/kg can be lethal to adults [1], so it has been prohibited from application in China through an explicit order since 2016. However, clinical studies have still found application of PQ-contained herbicides in other forms, because there are occasional poisoning patients due to self-administration or accidental administration of it. Each year witnesses 33.3% of suicide cases due to PQ, and 97.69% are self-poisoning cases [2]. A clinical study has pointed out that among

cases with acute PQ poisoning, the successfully rescuing rate is low with a mortality rate over 70.0%, and 40.0%-60.0% of them died of MODS (Multiple Organ Dysfunction Syndrome) within 24-72 h after poisoning [3].

Lung is the main target organ of acute PQ poisoning and also the trigger organ of MODS. Generally, it is damaged within one week after PQ poisoning. The first manifestation of PQ poisoning is acute alveolitis, and the imaging manifestations are alveolar edema, inflammatory cell infiltration and rapid pulmonary interstitial fibrosis. At the current stage, clinical data have confirmed that refractory hypoxemia caused by pulmonary fibrosis is the main cause of death due to PQ, so the lung is the primary and important therapeutic target organ for successful rescue. In addition, the survived patients often suffer from severe pulmonary fibrosis that repeatedly gives rise to hypoxemia and thus seriously compromises their quality of life [4]. However, the specific mechanism of PQ-induced acute pulmonary fibrosis is still unclear. The main pathological mechanisms involve alveolar injury and alveolar epithelial cell remodeling, which may be related to factors such as activation of transforming growth factor β1 (TGF-β1) and excessive deposition of extracellular matrix (ECM). Pirfenidone (PFD) is a small molecule cytokine inhibitor and one pyridone compound. It is able to inhibit fibroblast activity by regulating various factors and fight against fibrosis, scar formation, inflammation, and oxidation. The main indication of PFD is lung-specific fibrous disease, and it has achieved clinical results in liver fibrosis primarily [5]. The data suggest that PFD can prevent and treat fibrosis of lungThis study explored the efficacy of PFD in acute PQ poisoning and its related mechanism, with the goal of providing guidance for clinical treatment of the poisoning.

Materials and methods

General data

A total of 86 patients with acute PQ poisoning admitted to our hospital from February 2018 to February 2020 were analyzed retrospectively. The patients were assigned to the PFD group or the Non-PFD group according to whether they received PFD treatment (at 200 mg/time, 3 times/day) for 6 months after discharge. This study was approved by the Ethical Committee of our hospital.

Inclusion criteria: Patients who met relevant diagnostic criteria in the 2013 Expert Consensus on Diagnosis and Treatment of Acute Paraquat Poisoning and were confirmed with pulmonary fibrosis; patients who were poisoned through digestive tract due to oral administration, and visited a doctor within 24 h after poisoning; patients poisoned with a dose of 20.0% PQ solution <40 mL; and patients who met the indications of the selected treatment plan, had no history of allergy to the selected drugs, and successfully received the standard 21-day treatment based on “Taishan Consensus” [6]. Exclusion criteria: Patients poisoned through skin contact or consumption of PQ-contained foods; patients >75 years old; patients with comorbid chronic obstructive pulmonary disease or bronchoscope; patients who died within the treatment cycle; and patients without detailed clinical data.

Methods

After admission, all patients in the two groups received the standard 21-day treatment based on “Taishan Consensus” successfully, including gastric lavage with 2.0% sodium hydroxide solution in the early stage (within 72 h after poisoning), catharsis with 200 mL 20.0% mannitol (Shandong Tianli, H20073706), urination with diuretics (Beijing Novartis Pharmaceutical Co., Ltd., H20040217), and HP (hemoperfusion) combined with HD (hemodialysis) immediately after gastric lavage. Additionally, they were also injected intravenously with adequate glucocorticoid, and 500-1000 mg methylprednisolone (Tianjin Tianan Pharmaceutical Co., Ltd., H2010-3047) was the first choice. Moreover, they were also given adjuvant therapy including reasonable oxygen therapy, mechanical ventilation, gastrointestinal nutrition support, liver protection and bile secretion promotion, kidney protection drugs, and symptomatic treatment.

After the standard 21-day treatment based on “Taishan Consensus”, patients in the PFD group orally took PFD capsule (Beijing Continent Pharmaceutical Co., Ltd., China, 100 mg) at an initial dose of 200 mg/time, 3 times a day. If the drug caused no obvious side effects, the dose was increased to 400 mg/time and 3 times a day after 3 days of treatment, and

drugs were all taken within 1-2 h after meals. After 6 months of continuous treatment, the drug should be stopped in time if it gave rise to intolerable side effects. For patients without disease alleviation after 6 months of treatment, the treatment should also be interrupted.

Outcome measures

Primary outcome measures: (1) The two groups were compared in pulmonary fibrosis-associated indexes including serum hyaluronic acid (HA), laminin (LN), type IV collagen (CIV), and type III procollagen (PCIII). Fasting peripheral fasting venous blood (5 mL) was sampled from each patient in the two groups before and after treatment, and then centrifuged at 3000 r/min for 10 min. All operations were completed within 2 h, and the collected serum was stored in a refrigerator at -20 for later testing. Additionally, a Roche E601 automatic electrochemiluminescence immunoassay analyzer was used to determine pulmonary fibrosis-associated indexes such as HA, LN, CIV and PCIII, and the kits were all purchased from Wuhan Aidikang Biotechnology Co., Ltd. (2) The two groups were compared in pulmonary function-associated indexes including forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC before and after treatment. A SFJ1000 pulmonary function testing equipment (Shanghai Hanfei Medical Equipment Co., Ltd., China) was adopted to determine pulmonary function-associated indexes including FEV_1, FVC and FEV_1/FVC. (3) The two groups were compared in arterial blood gas indexes including partial pressure of carbon dioxide (PCO_2), oxygen partial pressure (PO_2), and PaO_2/FiO_2 before and after treatment. A ST2000 blood gas analyzer (Wuhan Easydiagnosis Biomedicine Co., Ltd., China) was adopted to detect PaO_2 and $PaCO_2$, and PaO_2/FiO_2 was calculated.

Secondary outcome measures: (1) The two groups were compared in the number of cured patients, patients with symptom alleviation, dead patients, and effective treatment rate (The total effective rate = (the number of cured patients + the number of patients with symptom alleviation)/the total number of patients *100%). (2) The two groups were compared in the incidence of adverse reactions such as rash, gastrointestinal bleeding, nausea and vomiting, liver function damage, and kidney function damage (total incidence of adverse reactions = the number of cases with adverse reactions/the total number of patients *100%). (3) After 6 months of treatment, the Kaplan-Meier survival curves of the two groups were drawn and compared.

Efficacy criteria and testing methods

According to efficacy criteria in the 2013 *Expert Consensus on Diagnosis and Treatment of Acute Paraquat Poisoning*, the efficacy was divided into three grades [7]. Cured: The clinical symptoms and signs of the patient disappeared completely, and the results of chest CT and liver and kidney function indicators were normal. Alleviated: The patient showed only mild respiratory symptoms and biochemical indexes that basically returned to normal, and the Chest CT results of the patient indicated changes in pulmonary interstitium. Ineffective: Death. Effective treatment rate = (Number of cured patients + number of patients with symptom alleviation)/total number of patients *100%.

Statistical analyses

All statistical data were analyzed by SPSS 21.0 statistical software. Measurement data, expressed as the mean ± standard deviation, were compared between groups using the independent-samples T test and within groups before and after therapy using the paired t test. Enumeration data, expressed as case (percentage), were compared between groups using the χ^2 test. The Kaplan-Meier method was used to calculate the survival time, and corresponding survival curves were drawn and analyzed via the Log-rank test. Figures were drawn with GraphPad Prism 6 software. $P<0.05$ indicates a notable difference.

Results

Comparison of general clinical data between the two groups

The two groups were not greatly different in general data including gender, age, poisoning dose, time from poisoning to first gastric lavage, body mass index (BMI), and complicated basic diseases (all $P>0.05$, **Table 1**), so they were comparable.

Table 1. Comparison of General data between the two groups

Groups	NO-PFD group (n=43)	PFD group (n=43)	χ^2/t	*P*-value
Sex (n)			0.047	0.827
Male	24	25		
Female	19	18		
Age (years old)	32.6±10.8	32.4±11.3	0.079	0.937
Poisonous dose (mg/kg)	23.69±9.83	24.12±9.75	0.204	0.839
Time from poisoning to first gastric lavage (h)	3.26±1.53	3.30±1.49	0.136	0.882
BMI (kg/m^2)	23.61±3.15	23.56±3.23	0.114	0.913
Complicated underlying diseases			0.143	0.676
Hypertension	7	6		
Diabetes	5	5		
Hyperlipidemia	4	5		
Other	2	3		

Note: BMI: body mass index; PFD: pirfenidone.

Table 2. Comparison of effective treatment rate between the two groups (n, %)

Groups	Cured	Alleviated	Ineffective	Effective treatment rate (%)
NO-PFD group (n=43)	13 (30.23)	14 (32.56)	16 (37.21)	62.79
PFD group (n=43)	20 (46.51)	16 (37.21)	7 (16.28)	83.72
χ^2	2.409	0.205	4.807	4.807
P-value	0.121	0.651	0.028	0.028

Note: PFD: pirfenidone.

Comparison of effective treatment rate between the two groups

In this study, there was no patient lost to follow up, and there was no medication interruption or discontinue. The PFD group showed a notably higher total effective rate than the NO-PFD group (83.72% *vs.* 62.79%, χ^2=4.807, P=0.028, **Table 2**).

Comparison of pulmonary fibrosis-associated indexes between the two groups before and after treatment

Before treatment, there was no notable difference between the two groups in serum HA, LN, CIV, and PCIII (all P>0.05); however, after treatment, the PFD group showed notably lower levels of serum HA, LN, CIV, and PCIII than the NO-PFD group (all P<0.001, **Figure 1**).

Comparison of pulmonary function-associated indexes between the two groups before and after treatment

Before treatment, there was no notable difference between the two groups in FEV_1, FVC, and FEV_1/FVC (all P>0.05); however, after treatment, the PFD group showed notably higher levels of FEV1, FVC, and FEV_1/FVC than the NO-PFD group (P<0.001, **Figure 2**).

Comparison of arterial blood gas indexes between the two groups before and after treatment

Before treatment, there was no remarkable difference between the two groups in arterial blood gas indexes such as $PaCO_2$, PaO_2 and PaO_2/FiO_2 (all P>0.05); however, after treatment, the PFD group showed notably higher PaO_2 and PaO_2/FiO_2 levels than the NO-PFD group (both P<0.001), but the level of $PaCO_2$ in the PFD group was lower than that in the NO-PFD group in (P<0.05; **Figure 3**).

Comparison of the incidence of adverse reactions between the two groups

There were no significant differences in incidence of adverse reactions such as rash, gastrointestinal bleeding, nausea and vomiting, liver function damage and kidney function damage between the two groups (67.45% vs. 58.14%, P>0.05, **Table 3**).

Comparison of survival rate between the two groups

Based on 6 months of follow-up, Kaplan-Meier survival curves were drawn and analyzed by the

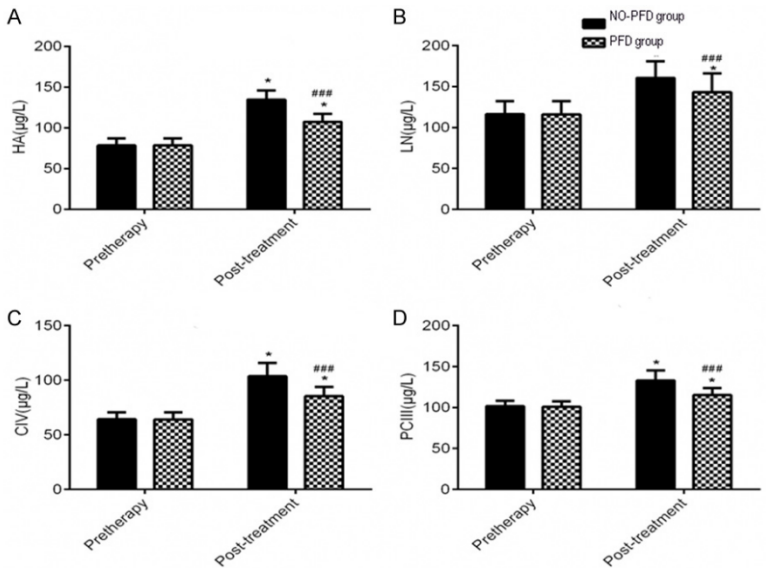

Figure 1. Comparison of pretherapy and post-treatment pulmonary fibrosis-associated indexes between the two groups. A: HA; B: LN; C: CIV; D: PCIII. Compared with pretherapy, *P<0.05; compared with the NO-PFD group, ###P<0.001. HA: Serum hyaluronic acid; LN: Laminin; CIV: Type IV collagen; PCIII: Type III procollagen; PFD: pirfenidone.

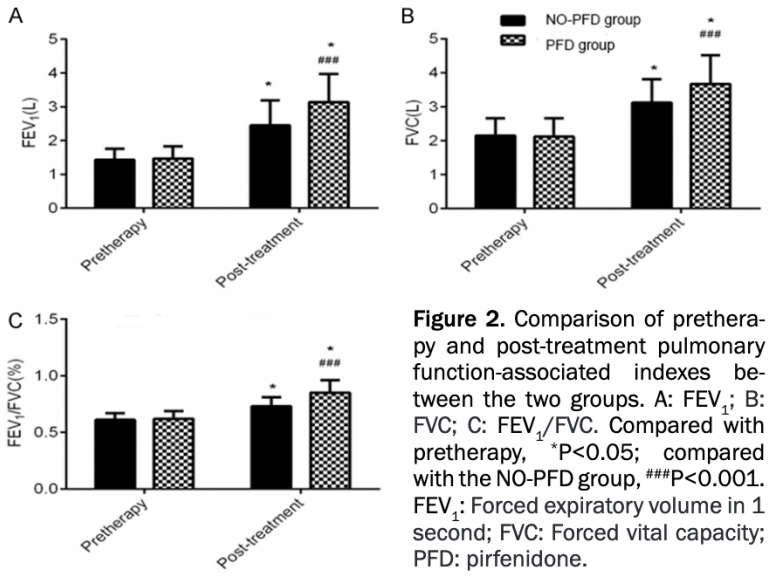

Figure 2. Comparison of pretherapy and post-treatment pulmonary function-associated indexes between the two groups. A: FEV_1; B: FVC; C: FEV_1/FVC. Compared with pretherapy, *P<0.05; compared with the NO-PFD group, ###P<0.001. FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; PFD: pirfenidone.

Log-rank method, and it was found that the survival rate in the PFD group was significantly higher than that in NO-PFD group (χ^2=5.168, P=0.023, **Figure 4**).

Discussion

The specific mechanism of pulmonary injury caused by acute PQ poisoning is still under investigation. In the early stage, acute PQ poisoning mainly gives rise to pulmonary injury, while in the middle and late stage, it gradually causes irreversible pulmonary fibrosis [8, 9]. According to a pharmacological study [10], oxygen free radical injury and inflammatory reaction may be the main pathogenesis of pulmonary injury. Alveolar cells have a strong ability to absorb and accumulate PQ. After being reduced to produce oxygen free radicals, PQ reacts with oxygen molecules to form superoxide compounds. The continuous oxidative stress can destroy the structure of mitochondria and then reversibly produce PQ molecules, forming a vicious circle that aggravates alveolar cell injury. Additionally, PQ can stimulate effector cells to express inflammatory mediators, including interleukin (IL) and tumor necrosis factor-α (TNF-α), and even give rise to systemic inflammatory cascade reaction, eventually causing alveolar cell damage [11]. Alveolar injury leads to capillary rupture, hemorrhage and edema, cell structure destruction and degeneration, exudation of cytoplasm, inflammatory cells and red blood cells, destruction of alveolar epithelial structure, and large amount of cellulose exudation to form a transparent membrane. In addition, it gives rise to a decrease in damaged type II alveolar epithelial cells, alveolar collapse due to the lack of surface-active substance, increased fibroblasts in the interstitium, and gradual filling of collagen in alveolar cavity, and finally promotes the development and progression of pulmonary fibrosis [12].

PFD is a new broad-spectrum anti-fibrosis pyridone drug, with multiple effects such as anti-inflammation, anti-oxidation and anti-fibrosis

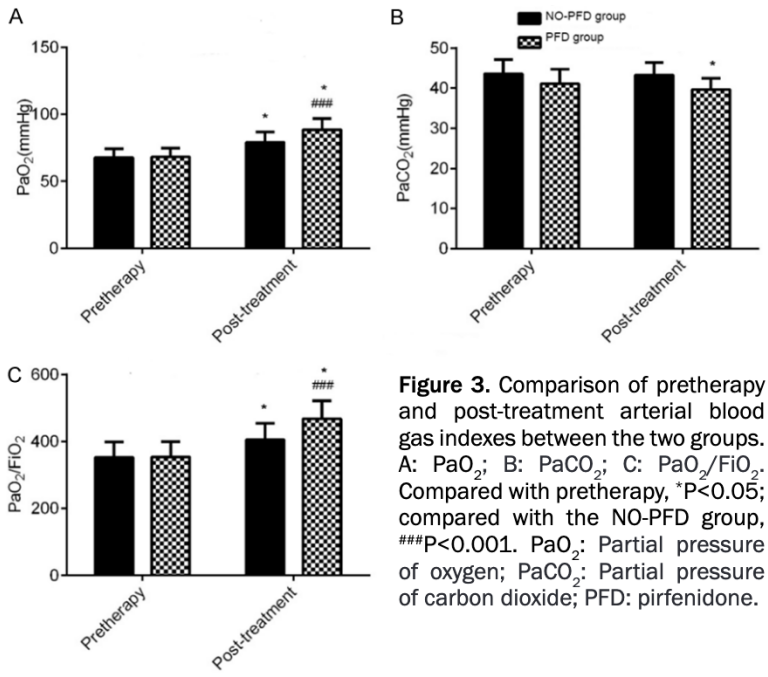

Figure 3. Comparison of pretherapy and post-treatment arterial blood gas indexes between the two groups. A: PaO_2; B: $PaCO_2$; C: PaO_2/FiO_2. Compared with pretherapy, $^*P<0.05$; compared with the NO-PFD group, $^{###}P<0.001$. PaO_2: Partial pressure of oxygen; $PaCO_2$: Partial pressure of carbon dioxide; PFD: pirfenidone.

Table 3. Comparison of the incidence of complications between the two groups (n, %)

Groups	NO-PFD group (n=43)	PFD group (n=43)	χ^2	P
Rash	2 (4.65)	7 (16.28)	3.102	0.078
Gastrointestinal bleeding	0 (0.00)	1 (2.33)	1.012	0.314
Nausea and vomiting	4 (9.30)	6 (13.95)	0.453	0.501
Liver function damage	11 (25.58)	8 (18.60)	0.608	0.436
Kidney function damage	8 (18.60)	7 (16.28)	0.081	0.776
Total incidence rate (%)	58.14	67.45	1.631	0.159

Note: PFD: pirfenidone.

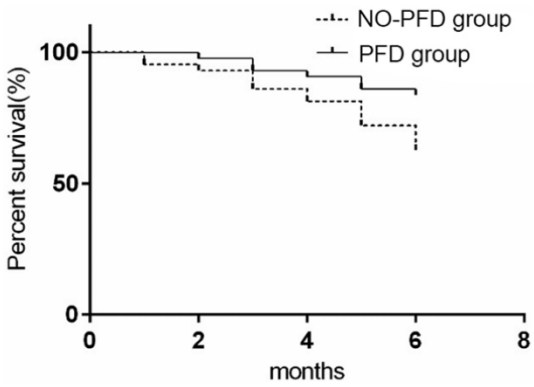

Figure 4. Comparison of Kaplan-Meier curves between the two groups.

effects. It can inhibit the expression of heat shock protein (HSP), TIMP-1 and TGF-p in fibroblasts, reduce their activity and collagen synthesis, and prevent some epithelial-mesenchymal transition, and thus controlling the fibrosis process [13]. A study by Li G et al. has revealed that PFD can hinder the accumulation of lymphocytes and eosinophils in the lungs, down-regulate inflammatory mediators such as IL-5 and IL-13 in alveoli, and lower the activities of NK cells and macrophages, avoid excessive aggregation of inflammatory cells, and alleviate fibrosis through anti-inflammation [14]. PFD can also exert a strong antioxidant effect by scavenging oxygen free radicals, alleviating oxidative stress, and inhibiting lipid peroxidation and the activity of its final products [15]. Moreover, PFD can be absorbed easily and is able to get wide distribution after entering blood and permeate blood-brain barrier. Therefore, it has become a new choice for the treatment of various types of pulmonary fibrosis. Furuya K et al. have conducted a multicenter, large-sample randomized controlled study, finding that PFD can help effectively delay the process of pulmonary fibrosis in patients with IPF (idiopathic pulmonary fibrosis), improve pulmonary function-associated indexes and blood oxygen status, with a controllable safety [16]. Currently, there are few clinical reports on the application of FPD in acute PQ poisoning, but basic research shows that PFD can down regulate TGF-β1 protein and collagen in lung tissue of mice with acute PQ poisoning, and thus inhibit the progress of pulmonary fibrosis [17, 18]. HA, an acidic mucopolysaccharide, can be expressed in large quantities in lung interstitial cells and fibroblasts after being stimulated. LN is a non-collagen glycoprotein in basement membrane, which can activate inflammatory cells, stimulate the expression of inflammatory factors and promote the synthesis of collagen fibers in pulmonary fibrosis. In addition, CIV and

PCIII can effectively reflect the synthesis and aggregation of collagen fibers in lung tissues, which are both verified to be sensitive evaluation indicators of pulmonary fibrosis [19]. In our study, the PFD group showed notably lower levels of serum HA, LN, C IV and PCIII than the NO-PFD group after treatment, suggesting that PFD could effectively prevent the development of pulmonary fibrosis. Additionally, the PFD group showed notably higher levels of FEV_1, FVC, and FEV_1/FVC than the NO-PFD group and also presented notably higher levels of PaO_2 and PaO_2/FiO_2 than the NO-PFD group, suggesting that PFD was able to effectively improve the pulmonary function and promote the exchange of oxygen in lung. Moreover, the PFD group presented a notably higher total effective rate than the NO-PFD group, and the survival curve of the PFD group was greatly better than that of the NO-PFD group after 6 months of follow-up. The results indicate that PFD is able to improve the treatment and prognosis of patients with acute PQ poisoning, and its ability is strongly bound up with its control on pulmonary fibrosis and its improvement to pulmonary function.

According to a current study, PQ can exert toxic effects on tissues and organs through various mechanisms, including mitochondrial damage, inflammatory damage and enzyme damage [20]. Kidney is the main excretory organ of PQ, and PQ-induced acute kidney damage (AKI) is mostly acute proximal tubular necrosis that causes damage to kidney reabsorption function and more severe poisoning due to accumulation of various substances in the body, and even leads to death due to acute kidney failure [21]. PQ can also gather in the liver, mediate inflammatory reaction, DNA damage and oxidative damage, and finally result in cholestatic liver injury by damaging interlobular bile ducts [22]. Avoiding aggravation of liver and kidney function damage in patients with acute PQ poisoning is the key to ensure good prognosis. PFD has been gradually popularized in the treatment of pulmonary fibrosis, and its drug safety has captured great attention. As an oral drug, PFD can give rise to digestive tract symptoms such as nausea and vomiting, and it has been found to be able to absorb ultraviolet rays with wavelengths of 290-320 nm and 320-340 nm, causing skin damage such as rash, but there is no clear report on its impact on liver and kidney function. In our study, there was no notable difference in the incidence of adverse reactions such as liver and kidney function damage, digestive tract symptoms and rash between the two groups, suggesting high safety of PFD due to its feature of not aggravating liver and kidney function damage [23]. PFD has been verified to be able to improve treatment on and prognosis of patients with acute PQ poisoning, with a good drug tolerance, so it is expected to be a brand-new treatment choice.

However, there are still some limitations in this study. FDue to the small sample size, the safety of PFD treatment has not been evaluated in detail. In addition, the efficacy of PFD has been evaluated, but the mechanism has not been explored which needs further study.

To sum up, PFD combined with HP+HD can effectively inhibit the process of pulmonary fibrosis, improve the pulmonary function of patients, reduce the damage to liver and kidney function, and thus improve the treatment efficacy and prognosis of patients with acute PQ poisoning.

Disclosure of conflict of interest

None.

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