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# Acute lung injury mechanism and therapy induced by paraquat poisoning

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## ABSTRACT

Paraquat (PQ, methyl viologen) was widely used in agricultural production throughout the world in 1962 for its efficient herbicidal activity. PQ was also highly toxic drug. About 5 mL medicine including 20% paraquat was life-threatening that can cause poisoning. In 1966, some people died because of PQ poisoning. Most patients had acute respiratory distress syndrome after 2 wk, and 70% of them died due to the lack of effective detoxification drugs. Thus, it was particularly important to understand the pathogenesis of PQ poisoning and give some effective treatments. This article will review the toxicological mechanism and treatment on PQ poisoning of acute lung injury.

## 1. Toxicological mechanism of paraquat (PQ) poisoning of lung injury

PQ concentration in the lung tissue reached its highest after 15 h of oral paraquat, which was 10-90 times the plasma concentration[1]. This is due to the presence of polyamine transport system in the lungs that is located at epithelial cells of alveolar type I, alveolar type II cells and Clara cells[2]. PQ, with similar structure to polyamines, is transported and utilized by those cells with effects on cellular energy metabolism, which is more pronounced under aerobic conditions[3]. This ingestion has energy dependence and time dependence[4]. PQ can cause cell damage by diffusing into pulmonary macrophages, interstitial cells and pulmonary vascular endothelial cells[5]. Following will introduce some current theories related to toxicological mechanism of paraquat poisoning of lung injury.

### 1.1. Oxidative stress theory

Oxidative stress injury is currently the most in-depth study and also one of the main mechanisms of paraquat-induced lung injury. PQ exists as a bipyridyl cation in serum and is actively taken up by the lungs following by a redox reaction that produces a large amount of reactive oxygen species[5]. After PQ getting into the lungs, a large amount of oxygen radicals and superoxide anion are produced under the action of nicotinamide adenine dinucleotide phosphate (NADPH) to form monovalent cation PQ, which then reacts with molecular oxygen to form divalent cations[6]. It results in the existence of a large number of intracellular reactive oxygen species, which damages cell membrane of organelle in mitochondria and causes apoptosis; in the meantime, a large number of hydrogen peroxide generates and reacts with ferrous ions to form OH<sup>-</sup>, which damages alveolar epithelial and vascular

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endothelial cells, causing changes in membrane structure and function[6]. The whole process consumes lots of NADPH, which affects intracellular tricarboxylic acid cycle process and inhibits ATP production[7].

### 1.2. Mitochondrial damage theory

PQ poisoning would produce lipid peroxide[8]. Lipid peroxidation would increase mitochondrial membrane permeability and cause mitochondrial swelling, thus damaged the mitochondria leading to apoptosis of alveolar epithelial cells and pulmonary vascular endothelium cells[9]. Calcium overload also plays an important role in PQ poisoning, which may be related to the abnormal opening of voltage-dependent calcium channel on mitochondrial membrane, leading to the deposition of phosphate in cytoplasm[10]. This will aggravate the destruction of mitochondrial structure and function. Calcium overload may be one of the important mechanisms leading to acute lung injury (ALI) caused by mitochondrial injury of acute PQ poisoning[5].

### 1.3. Inflammatory mediators theory

In early stage of PQ poisoning, a large number of inflammatory cells and immune cell would infiltrate the poisoned place[11]. PQ poisoning first to cause ALI, which had a large number of inflammatory cells gathering in the alveoli and mainly were alveolar macrophages cells, neutrophils *etc.* Alveolar macrophages cells could synthesize and release a large number of cytokines, inflammatory mediators, chemokines and proteases *etc.*, leading to pejorative inflammation and injury of lung tissues. After PQ poisoning, inflammation occurred on the third day; percolate in the alveoli and hypertrophic fibroblasts began to accumulate on the seventh day, on which hypertrophic fibroblasts secreted collagen fibers and pulmonary fibrosis appeared; and normal alveolar structure was destroyed on day 14[12]. Thus, inflammatory cells played an important role in the occurrence of PQ-induced ALI.

### 1.4. Interstitial cell proliferation theory

Song *et al*[13] found that alveolar epithelial cells declined in earlier stage of PQ poisoning, but basal cells remained normal. Later, basal cells were also damaged, and interstitial cells proliferated into the alveoli leading to the formation of alveolar fibrosis. After these pathological changes, most of the alveolar wall remained intact. Alveolar fibrosis may result from epithelial cells damage and basal cell damage, as well as proliferation of interstitial cells.

### 1.5. Cytokines theory

PQ poisoning activated a large number of cytokines and caused lung injury. Expression of transforming growth factor- $\beta$  (TGF- $\beta$ ) was significantly increased in PQ poisoning-induced model of pulmonary fibrosis[14], and TGF- $\beta$  was considered as the

initiating hub of pulmonary fibrosis[15]. TGF- $\beta$  1 was secreted by macrophages in the early stage of PQ poisoning, which can promote the transformation of fibroblasts into myofibroblasts[16]; the latter interacted with pulmonary interstitium to promote the secretion and proliferation of mesenchymal stem cells; which can coordinate the role of other cytokines through paracrine effects, such as platelet-derived growth factor, insulin-like growth factor-1, interferon- $\gamma$  *etc.*, to mediate the early acute inflammatory reaction and advanced fibrosis. It can be found in lung and bronchoalveolar lavage fluid of PQ poisoning rat that monocyte inflammatory factor-2, interferon- $\gamma$ , and tumor necrosis factor- were significantly higher than in control group[17].

### 1.6. DNA damage and apoptosis theory

PQ poisoning mechanism has been deep into the molecular and gene expression levels that DNA base changes and the destruction of the spiral bimolecular structure. PQ poisoning causes the production of a large number of oxygen free radicals, which is bad for DNA and can induce karyopyknosis and DNA strand breakage[18]. PQ may induce cell damage by activating apoptosis signal regulating kinase-1[19].

## 2. Treatment methods

Many researches were done on the treatment of PQ poisoning, but the effect was not ideal[20]. The mortality is still very high. Three methods are recognized as the cornerstones of acute PQ poisoning treatment including early removing unabsorbed PQ residue, blood purification, and the application of immunosuppressive agents.

### 2.1. Toxic excretion

Some measures can be taken to prevent the continuous absorption of PQ including cleaning, gastric lavage, adsorption, and catharsis *etc.* PQ level in plasma was directly related to the prognosis of PQ poisoning patients. In addition to routine infusion and diuretic, the methods of hemodialysis, plasma perfusion and continuous venous filtration *etc.* could promote PQ discharge in blood. As these technologies were in their infancy, their effects needs to be confirmed through further clinical validation.

### 2.2. Drug treatment

#### 2.2.1. Application of hormones and immunosuppressive agents

Most scholars believed that the application of corticosteroids and cyclophosphamide in the treatment of PQ poisoning was a major breakthrough. Adreno cortico hormones had effects of anti-inflammatory, inhibiting neutrophil, accumulation and adhesion with lymphocyte in the lungs, as well as anti-lipid peroxidation *etc.* Cyclophosphamide played a role in all aspects of immunity of cells and humoral, with a strong anti-inflammatory effect.

### 2.2.2. Anti-oxidative therapy

Currently, most in medical profession thought that oxidative stress was one of the important mechanisms of PQ poisoning, and thus they recommended anti-oxidative therapy as a main treatment. Antioxidants such as edaravone, ambroxol, quercetin, acetylcysteine[21], vitamin C, *etc.*, had influences on improvement of PQ poisoning. They can not significantly reduce the mortality rate, but had a certain effect on prognosis improvement and fibrosis inhibition.

### 2.3. Other treatments

There are some other treatments including symptomatic therapy, supportive treatment, oxygen therapy as well as lung and mesenchymal cells transplantation. Although no successful treatment case of lung transplantation had been reported yet, this method reported by Bertram *et al*[22] could be considered at the critical moment and complete PQ removal *in vivo* may be achieved. Tsai *et al*[23] reported that mesenchymal cells transplantation could improve the efficacy of PQ poisoning treatment, and they thought this treatment may be a promising one. In addition, adjuvant therapy of salicylate[24], ozone[25] also had a certain effect on PQ poisoning, while further evidence-based clinical validation is needed

## 3. New ideas of treatment

### 3.1. Amifostine (AMF)

AMF was a thiophosphate nucleophilic precursor. It functioned as the cytoprotective agents and anti-nuclear radiation protector that protected hematopoietic stem cells in bone from damages of chemotherapeutic agents, accelerated proliferation of stem cells, and improved noxiousness accumulation in cells. AMF was a radioprotectant for the treatment of adverse reactions to chemotherapy and radiotherapy[26], with effects of cleaning free radicals in tissue and anti-oxidant[27]. In addition, AMF was similar to polyamines and PQ in molecular structure and could be used as a pseudo-polyamine to participate in chemical processes[28]. AMF significantly prolonged survival time of mice with acute PQ poisoning, which may be able to combat the oxidation of PQ *in vivo*[29]. Brandok *et al*[27] also believed that AMF could theoretically be used as an antidote to PQ poisoning, but experiments had shown no effect of AMF on mortality and lung histopathology in PQ poisoning mice. While some demonstrated that repeated dosing of certain AMF could prevent lung tissue from PQ uptake and thus reduce the inflammatory and oxidative damages[30].

### 3.2. Stem cells

At present, how to apply stem cells to clinical diseases is the hotspot in the medical field. Bone mesenchymal stem cells

(BMSCs) are adult stem cells that exist in bone marrow. They are deeply studied and have the potential of multidirectional differentiation and self-renewal, which are the ideal tools for tissue engineering and cell therapy. They can differentiate into many kinds of tissues under certain conditions, and they have been implanted into the treatment of various lung injuries in recent years. Some animal experiments showed that BMSCs had positive therapeutic effects on PQ-induced lung injury. BMSCs can differentiate into alveolar epithelial cells [ I and II ], bronchial epithelial cells and fibroblasts[31-33], and can also promote lung tissue repair[34,35]. BMSCs transplantation could inhibit the inflammatory response of early poisoning[36]. There were two methods related to BMSCs transplantation treatment on PQ poisoning-induced pulmonary fibrosis that firstly, BMSCs could migrate to damaged sites; and secondly, the transplantation of BMSCs could significantly reduce the content of TGF- $\beta$  in damaged sites[37], thus inhibit the formation of pulmonary fibrosis. However, some studies had shown that there were no significant effects of BMSCs on pulmonary fibrosis, and may even worsen the situation. Yan *et al*[38] showed that no significant change of pulmonary fibrosis was found in the BMSCs treatment group mice, and even myofibroblasts were generated deteriorating pulmonary fibrosis. Artificially controllable factors may have something to do with the paradoxical experiment results. BMSCs could be a new treatment for PQ poisoning, while the exact therapeutic effects were not clear yet. Further studies of BMSCs were required including studies about its potential acting mechanism, optimal infusion time, infusion doses and methods, as well as the safety.

## 4. Conclusion

In summary, the mechanisms of PQ-induced human pathogenicity are complicated, of which oxidative stress theory is currently the most in-depth study and is also one of the main mechanisms of PQ-induced ALI. PQ poisoning must be treated in multiple ways. Most of poisoning patients die of pulmonary fibrosis. It can be believed that treatment on preventing the formation of pulmonary fibrosis will become the most important issue in the future.

### Conflict of interest statement

The authors declare that they have no conflict of interest.

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