Systemic inflammatory response after paraquat poisoning

Mahrang Hedaiaty, Mahsa Hedaiaty, Rasoul Salimi

1Clinical Toxicology Department, Isfahan Clinical Toxicology Research Center, Noor Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
2Radiology Department, Imam Khomeini Hospital, Lorestan University of Medical Sciences, Broujerd, Iran
3Emergency Department, Besat Hospital, Hamedan University of Medical Sciences, Hamedan, Iran

Abstract
Paraquat is known as a toxic pro-oxidant herbicide, such as multi-organ failure, including the lung, kidney, liver and heart injuries. Although the exact underlying mechanism remains poorly understood, however some hypothesis have been suggested for paraquat toxicity. For instance, accumulation of free radical species, development of oxidative stress and mitochondrial dysfunction. In this mini-review we will summarize the role of inflammation in paraquat that induced lungs, heart, kidney and liver injury. Cellular mechanisms behind paraquat toxicity are discussed with a focus on oxidative stress, mitochondrial injury, lipid peroxidation, tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS) and autophagy. Also, special attention is given to the inflammatory reaction triggered by paraquat exposure in organ damage.

Keywords: Paraquat poisoning, Inflammation, Oxidative Stress, Mitochondrial Injury, Lung, Kidney, Liver, Heart

Introduction
Paraquat (1, 1'-dimethyl-4, 4'-bipyridinium dichloride), an herbicide which can effectively and rapidly dry plant, is also highly toxic to human. Paraquat is a substance that belongs to pyridine, which is rapidly deactivated in earth, but can be absorbed by skin, digestive tract and respiratory tract (1). Acute paraquat poisoning remains a major cause of death from both accidental and voluntary ingestion, in developing countries, because of lack of specific and effective treatment for it (2,3). Paraquat mainly deposits in lung which can lead to diffused lung injury and resulting an increased inflammatory process to pulmonary fibrosis (4). The development of pulmonary fibrosis, resulting in dyspnea, cyanosis, respiratory distress and death due to respiratory failure (3). Furthermore, it can damage organs such as heart, liver and kidney, thus leads to multiple organ dysfunction syndrome. There is no specific treatment for it yet, however control of inflammatory infiltration with, anti-inflammatory and immunosuppressive drugs is suggested as the key to save patient’s life (2,3,5).

Materials and Methods
For this mini-review, we used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents; paraquat poisoning, inflammation, oxidative stress, mitochondrial injury, lipid peroxidation, tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS) and autophagy. Also, special attention is given to the inflammatory reaction triggered by paraquat exposure in organ damage.

The mechanisms of inflammation in paraquat poisoning
The mechanism of acute paraquat toxicity remains unclear, however the inflammatory reactions by continuing influx of neutrophils that release cytotoxic enzymes, free radicals and inflammatory mediators have major role in extensive collateral damage to surrounding tissue. Paraquat induces oxidative stress by production free oxygen radicals by consumption of intracellular nicotinamide adenine dinucleotide phosphate undergoes a redox cycling reaction in mitochondrial matrix and causing...
lipid peroxidation of the cell membrane then cell death and consequent inflammatory reaction (2,5,6). On the other hand, fragments of tissue degradation delivers proteases and various reactive oxygen species into the wound environment which induce oxidative stress lead to detrimental cytotoxic effects (6). Some researchers and clinicians have used antioxidants as a treatment modality for paraquat toxicity such as vitamin E and N-acetylcysteine and vitamin C in humans and animals, but these treating have failed to modify the toxicity of paraquat mainly to their inability to cross cell membrane barriers or their rapid clearance from cells (3,7).

According to a review of previous studies; after entering paraquat to the body, it can affect the protein synthesis function of endoplasmic reticulum dysfunction and activation of sterol regulation cascade reaction to maintain homeostasis following disequilibrate the homeostasis, autophagy and apoptosis. In addition, the endoplasmic reticulum injury can cause inflammatory infiltration, edema and hemorrhage in alveolar septum. The neutrophils accumulate in bronchoalveolar. The inflammatory cells produce reactive oxygen species and protolithic enzymes, then leading to the development of pulmonary fibrosis (5,8). In addition, oxidative stress associated to paraquat poisoning caused neutrophilia that triggered a rise in the concentration of tumor necrosis factor (TNF-α). The inducible nitric oxide synthase (iNOS) is an isoform of nitric oxide synthases that is involved produces nitric oxide as an immune defense mechanism. The level of iNOS expression in paraquat-poisoned vascular was increased around four fold higher in rat and iNOS was caused vascular dysfunction. TNF-α was relevant for iNOS expression (7-9). Hence, paraquat consumption can cause vascular and dysfunction pulmonary and systemic inflammation.

Furthermore, a survey showed that arachidonic acid which is an important part of inflammatory metabolic pathways, reduced paraquat-induced upregulations of inflammatory mediators such as TNF-α, interleukin (IL)-1β IL-6, and II-8 and upregulation increased the levels of anti-inflammatory cytokine and antioxidant enzymes. Therefore, arachidonic acid can play a potent protection role against acute lung injury and ameliorate pulmonary edema, deteriorated oxygenation and inflammation (10).

**Target organ injury in paraquat poisoning**

The lung is an affected main target organ in paraquat toxicity. Paraquat is actively accumulates in the alveolar type I and II epithelial cells of lung tissue by an active polyanmine uptake transport systems. Pulmonary concentration of paraquat may be 6 to 10 times higher than plasma concentration of paraquat and paraquat is reserved in the lungs even when blood levels start to decrease. Paraquat increases the permeability of the alveoli-capillary unit, leading to rise in the systemic circulation, damage in alveolar type I and type II epithelial cells in destructive phase and alveolitis, inflammatory cell infiltration and pulmonary edema in proliferative phase. It induces acute lung injury by both an increase in oxidative stress and inflammatory response. Delayed re-epithelialization of the alveolar surface may lead to pulmonary fibrosis (2,6).

Acute and chronic inflammation often trigger a complex cascade of cellular responses that leads to tissue fibrosis and ultimately to end-organ failure. Delayed re-epithelialization of the alveolar surface can be effective in pulmonary fibrosis (4). Many paraquat-poisoned patients develop acute respiratory distress syndrome that often has high incidences of mortality and morbidity (11). A previous study demonstrated that partial pressure of oxygen in arterial blood, fractional inspired oxygen (PaO2/FiO2), platelet count, serum bilirubin concentration, Glasgow coma score, hypotension, serum creatinine or urine output, blood paraquat concentrations and steroid and cyclophosphamide pulse therapies were significant predictors for acute respiratory distress syndrome at 48 hours after paraquat poisoning (3,12). Paraquat is rapidly distributed with high concentration in the kidneys and largely excreted to urine within 12–24 hours. But its excretion is limited due to nephrotoxicity is very common in paraquat intoxication. Furthermore, renal dysfunction leads to decreased renal Paraquat clearance which helps great toxicity in other organs. Therefore, acute kidney injury rises the severity of pulmonary toxicity, multi-organ failure and death (3,11,13).

Urinary kidney injury molecule-1, urinary cystatin C and urinary albumin elevations correlated with the degree of renal damage and injury development as could predict the degree of overall kidney injury in rat paraquat model (13). Retrospective analyses of 120 patients with paraquat poisoning were showed that the lower serum potassium concentrations were significantly associated with a high mortality rate. Hypokalemia in paraquat poisoning maybe induced by renal potassium depletion causing decreased potassium reabsorption, and direct oxidative injury in renal tubules. However, hypokalemia could be a poor prognostic factor in early evaluation of prognosis in these patients (14).

There are several cardiovascular effects reported with paraquat poisoning. The sever patients usually suffer from hyperdynamic circulation. Cardiovascular collapse and multiple organ failure have been known as the immedi-
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ate causes of death. Acute paraquat poisoning may cause direct myocardium injury, toxic myocarditis or the sinus node dysfunction (3,11). A previous study demonstrates that corrected QT prolongation in the electrocardiogram, serum bicarbonate level, hyperglycemia and elevated heart rate were observed more frequently in non-survivors than in survivors of acute paraquat poisoning. Also corrected QT prolongation might predict mortality notwithstanding of normal potassium levels (7,15). Myocardial necrosis, interstitial edema, vascular congestion, marginalized leukocytes within capillaries and localized hemorrhagic infiltration have been reported in the postmortem heart examination secondary to paraquat intoxication (7). According to a study on 14 autopsy cases of paraquat poisoning; paraquat could also cause hepatocytic and bile duct injury. The pathogenesis of which was not clearly understood. The bile duct injury was produced by a direct corrosive effect of paraquat and the infiltration of neutrophils and histiocytes in the intraductal and periductal tissues (16). Another study showed hepatocellular apop
tosis and inflammatory cytokines expression and their mechanisms after paraquat poisoning in rat. Paraquat could cause acute liver injury association with TNF-α and iNOS (17).

Conclusion
Paraquat induces systemic inflammation, characterized by neutrophilia. Also, it accumulates preferentially in lungs and elevated pulmonary neutrophil influx, raised circulating levels of TNF-α, iNOS and causes oxidative stress. Systemic inflammation associated to paraquat intoxication can cause cardiovascular, kidney, hepatocyte and bile duct injury. Inhibition of systemic inflammation can be useful in cases of paraquat poisoning.

Authors’ contribution
MH, MH and RS wrote the paper equally.

Conflicts of interest
The authors declared no competing interests.

Ethical considerations
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