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Paraquat Poisoning Management in Iran (Isfahan): Devising a Protocol

Mahrang Hedaiaty[1], Ali Mohammad Sabzghabaee[1], Farzad Gheshlaghi[1] and Nastaran Eizadi-Mood[1*]

[1]Department of Clinical Toxicology, Isfahan Clinical Toxicology Research Center, Noor Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MH, NEM, FG and AMS designed the study. Author MH wrote the protocol and wrote the first draft of the manuscript. Author MH managed the literature searches. All authors read and approved the final manuscript and are responsible for the whole manuscript.

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ABSTRACT

Background: Paraquat poisoning has been a health concern in many developing countries. Management of it is not standardized and varies from center to center. This study is aimed at devising an available evidence-based comprehensive protocol for parquat poisoning management in Isfahan, Iran, to reduce unnecessary variations in practice.
Materials and Methods: A narrative search in electronic databases was performed. Several peer-reviewed articles, guidelines, and textbooks were reviewed and practical details were extracted from 1967 till now.
The simple, available and wide-ranged descriptive protocol was developed.
Then, it was finally discussed with expert physicians specialized to be optimized for the diagnostic tools and treatments used in this setting by supplementing other specific considerations.
Results: The final version of the protocol was designed in six steps. The algorithm consists of a planned are based on the severity of the toxicity. It comprised of supportive treatments based on Resuscitation, Gastrointestinal decontamination, Elimination enhancement, and other treatment options for PQ lung injury.

**Corresponding author: E-mail: izadi@med.mui.ac.ir;*

Conclusion: Paraquat poisoning is a clinical toxicologic emergency, which needs to be diagnosed and treated in an organized manner, although its mortality rate is great.

Keywords: Clinical protocols; emergency treatment; paraquat poisoning; guideline.

1. INTRODUCTION

Paraquat (N, N´-dimethyl-4, 4´-bipyridinium dichloride; PQ) is a herbicide which was used in agriculture from 1962 [1]. Poisoning with PQ has been an important public health concern with high morbidity and mortality in Iran as worldwide [2-7]. Patients ingest PQ either intentionally as a suicide attempt or accidentally [8]. Intentional ingestion of this pesticide is a common dangers way of committing suicide in Isfahan as well [6,9].

Many case fatality of PQ is caused by its inherent toxicity and the lack of any effective treatment [6]. There is still no widely accepted guideline on management of PQ poisoning and the treatment varies in different area from supportive care alone to using various combinations of anti-oxidant, immune-modulation, hemodialysis, etc. [10,11]. Some of these treatments have been based on experiences of animal studies and case series conducted in different resource settings or insufficient documentation of toxicity severity. Therefore, this study was designed by our currently used protocol in the Isfahan Toxicology Center, by complying with scientifically information and amending the available protocols according to newer valid.

1.1 Pharmacokinetic

Absorption of PQ is limited following dermal and respiratory epithelium exposures [12]. The oral bioavailability of PQ varies is also estimated to be less than 5-10%during over a one to six hour period. PQ binds minimally to serum proteins, rapidly distributes to all tissues with distribution half-life of four to six hours and accumulates in alveolar cells [13,14]. The blood concentration peak occur ingot around six hours post ingestion. It initially is excreted by active secretion and may be detected in the urine as early as one hour after ingestion [15].

1.2 Pathogenesis

Mucosal lesions of the mouth, tongue, pharynx, esophagus and stomach are common in oral ingestion. PQ may cause erythema, blistering, ulceration, perforation, mediastinitis and pneumomediastinum [16,17].

1.2.1 Lung

The main organ affecting by PQ is lung. PQ selective accumulates in alveolar cells induces the production of many toxic free radicals such as reactive oxygen species, leading to lipid peroxidation of cell membranes, decreased nicotinamide adenine dinucleotide phosphate and cell necrosis [18,19]. In the acute destructive phase pulmonary edema may be happened due to acute alveolitis, diffuse alveolar collapse, vascular congestion, adherence of polymorph nuclear leucocytes and activated platelets to the vascular endothelium. Then it is followed by a proliferative phase that mononuclear profibroblasts filled the alveolar space, mature into fibroblasts during days to weeks and caused to lung fibrosis. The patient dies of severe anoxia [11,20,21].

1.2.2 Kidneys

In kidney, vacuolation in proximal convoluted tubules is followed by necrosis and renal failure develops quite rapidly. Acute tubular necrosis, glomerular and tubular hemorrhage, proximal tubular dysfunction may be present [22].

1.2.3 Liver

Congestion and hepatocellular injury occurs by endoplasmic reticulum degranulation and mitochondrial damage during hours to days after ingestion. It is demonstrated by jaundice and transaminase rising in liver function tests. Centrilobular hepatic necrosis and cholestasis may be also seen [23,24].

Ingestion of large amounts of liquid concentrate causes by edema, heart, renal, hepatic and cardiac failure. Patients with fulminate organ failure are suffered of hypoxia, shock and a metabolic acidosis. Death is occurred within several hours to a few days [10,25].

1.3 Clinical Manifestations and Prognosis

Three degrees of intoxication may be distinguished. There are some sub-groups in PQ lung injury progression that may be stopped or delayed by intensive treatment.

1.3.1 Mild poisoning

Patients have ingested less than 20 mg of PQ ion per kilogram body weight (mg/kg); they are asymptomatic or develop vomiting and diarrhea [26,27]. Generally these manifestations are ameliorated [28]. The kidney and liver toxicity is low and resolve within days. Lung injury would be similar to the airway restrictive disease.

1.3.2 Moderate to severe poisoning

Patients have ingested of 20 to 40 mg/kg of PQ ion. They may suffer vomiting, diarrhea and generalized symptoms such as lethargy, a widespread burning sensation, myalgia, generalized weakness, giddiness, headache, anorexia and fever. Fear, apprehension features, and restlessness are sometimes observed. After several days, dyspnea may be established in the most cases as the result of pulmonary fibrosis. Sometimes, renal failure and / or hepatic dysfunction may supervene [26,27].

Commonly, death occurs in most them during 2 or 3 weeks [29].

1.3.3 Acute fulminant poisoning

It happens following ingestion of more than 40 mg/kg of PQ. Ulceration of the oropharynx, nausea, vomiting, generalized symptoms and dyspnea is occurred early. Dyspnea may progress to the adult respiratory distress syndrome. Pneumothorax (in association with mediastinitis), pleural effusion and iatrogenic pulmonary edema may precipitate dyspnea [26,27,30]. Death may occur within 24 hours of poisoning duo to cardiac, respiratory, renal, hepatic, adrenal, pancreatic and neurologic failure [28].

Furthermore, PQ concentration-time data is extremely dangerous, so patients may succumb within short time following intoxication [31,32].

1.4 Diagnosis Testing and Paraclinical Finding

1.4.1 Dithionite urine test

The detection of PQ in serum, plasma and urine confirm PQ poisoning [29]. PQ serum level by high-performance liquid chromatography (HPLC) is influenced with the time of PQ ingestion, kinetics and organ injury [28,29,33]. Dithionite urine test with a weak alkalizing agent such as sodium bicarbonate is a diagnostic potential to determine the severity of PQ intoxication. The absorbance of it changes as a result of the blue color. It repeated every four hours until the results are negative [34].

1.4.2 Chest radiography (CXR)

Evaluation of PQ-induced lung injury by a simple chest radiograph has poor sensitivity and specificity. The CXR may be normal even in presence of multi-organ failure. Patchy infiltration of one or both lung may progress to an opacification fields. Therefore a high-resolution computed tomography (HRCT) of the lungs on the seventh day post-PQ ingestion is recommended. The inflammation of the alveoli that presents as ground glass opacity, progress to fibrosis within two or three weeks [35].

1.4.3 Arterial blood gas (ABG)

Arterial blood gas analysis indicates a low PaCO2 due to tachypnea.PaO2 decreases as the result of progression of lung injury and the restriction of lung volume [36].

1.4.4 Urine and blood tests

Within 24 hours of ingestion, Oliguria or non oliguric renal failure may event in severe toxicity, which results in increasing BUN and creatinine as well as proteinuria, glycosuria, microscopic hematuria, phosphaturiaand aminoaciduria. Excessive leaking of urate and sodium is also common [33,34]. Jaundice, hepatomegaly and abdominal pain may see to pancreatitis, with associated biochemical abnormalities including levels of pancreatic enzymes, amylase, lipase and blood sugar [37,38]. A polymorph nuclear leucocytosis, metabolic acidosis secondary to cardiovascular collapse and hypoxia and iatrogenic hypocalcaemia due to forced dieresis are another finding [26]. In the presence of renal impairment and muscle damage elevation of serum creatinekinase activity is seen [26].

1.4.5 Electrocardiogram (ECG)

Sinus tachycardia and nonspecific T-wave changes on electrocardiogram may occur. Bradycardia, hypotension, and cardiac arrest may supervene in severe toxicity [26].

2. MATERIALS AND METHODS

To design an instructive in-hospital algorithm for the management of PQ poisoning in adult patients (>16 years of age), a search in

electronic databases including Google scholar, EMBASE, MEDLINE, Scopus and TOXNET was performed, during the period of 1967 to 2016, using the following search terms: PQ AND algorithm, PQ AND protocol OR guideline and PQ AND Treatment. Our current protocol was the supplemented with useful details from the articles, guidelines; and textbooks were extracted. Then, a simple, available and wide-ranged descriptive protocol was developed.

Afterwards, the initial version of the protocol was discussed within a group comprised of medical toxicologists, clinical pharmacists, anesthesiologists and internal medicine specialists to fit our medical capacity in Iran. The final version of the algorithm was practiced for PQ poisoning cases.

3. RESULTS

The final version of the protocol was designed in six steps. The algorithm consists of a planned care based on the severity of the toxicity prediction including clinical manifestation, sodium dithionate urine test, plasma PQ concentration, amount of ingested PQ and the interval after ingestion. Because of the high mortality rate, all exposures should be observed in hospital for at least 24 hours post ingestion. It comprised of supportive treatments based on Resuscitation, Gastrointestinal decontamination, Elimination enhancement and other treatment options for PQ lung injury.

Steps 1 (Initial assessment and stabilizing the patient)

1. The victim should be reassured in agitated patients.
2. Immediate assessment of vital signs based on the standard principles of resuscitation (airway, breathing and circulation) should be done.
3. Assessing the need for intubation in patients with reduced level of consciousness without cough and gag reflex or serious respiratory distress.
4. The airway may break out due to mucosal toxicity or the aspiration of vomitus.
5. In mild to moderate hypoxia oxygen should not be delivered as it will worsen oxidative stress until the arterial PaO2 is less than 55.
6. Hypotension is occurred due to hypovolemia, so should be treated with infusion of crystalloid intravenous fluids (15–20 ml kg-1 in 20-40 min) and repeated as necessary until urine output is initially over 0.5 ml /kg considering renal function as well.
7. Vasopressors such as dopamine or norepinefrine may require if hypotention is not improvement.

Step 2 (Clinical monitoring and ongoing care)

1. Blood pressure, pulse rate, respiratory rate, auscultation of the lungs (for crepitations), measurement of peripheral oxygen saturation and body temperature should be checked at least a four-daily basis. In patients with unstable hemodynamic or respiratory failure, it must be checked every hour in Intensive care unit (ICU).
2. Close monitoring of hemodynamic parameters, urine output, arterial blood pressure, electrolytes balance and arterial blood gas was regularly done fluid with the aim of an acceptable urine output without overloading the patient.
3. If patient hasn't a normal level of consciousness, other reasons such as co-ingestion of other agents, hypoxia, hypovolemic shock and severe acidosis must be considered.
4. Clinical examination should be checked jaundice and right hypochondrial pain.
5. Mucosal oral injury maybe occurred and developed severe ulcers within a few days after PQ ingestion. So, prevent patients from taking oral feeding. Insert a nasogastric tube for adequate nutrition and relief pain with opiates if needed.
6. Determine biochemical states and organ function with laboratory analysis including: serum PQ level, complete blood cell counts, liver and renal function tests, urinalysis and arterial blood gas analysis every day.
7. ICU admission: The patient was admitted to ICU due to high risk of multi-organ failures.
8. Administrate antacids and intravenous proton pump inhibitors such as pantoprazole infusion 40 mg twice daily to all patients.
9. For patients with upper gastrointestinal irritation and bleeding should be administered higher doses of pantoprazole (8 mg/hour) and endoscopy should be performed within 12-24 hours.

Step 3 (Gastrointestinal decontamination and Extracorporeal elimination)

1. Receive gastric lavage for patients who present within one or two hours of post ingestion with a protected airway except gastro esophageal Perforation existence fallowing corrosive effect of PQ Swallowing.
2. Order to a single dose of activated charcoal or 1% bentonite solution except patients who are suffered of esophagus tissue damages caused by corrosive effect of PQ.
3. In PQ intoxicated cases with early kidney failure or high PQ plasma levels; Start the PQ elimination with hemoperfusion (HP) or hemodialysis (HD) within a few hours and continued until the detection of urine PQ was negative. Chose type of extracorporeal elimination based on patient's condition including renal function and electrolytes balance by available equipment.

Step 4 (Experimental therapy)

1. Vitamin E (a-tocopherol) could be administered as 300 mg intramuscular twice a day.
2. Infuse vitamin C (ascorbic acid) 150 mg/hour in 100 ml distilled water or dexstrose water 5%.
3. N-acetylcysteine (NAC) 150-300 mg/kg might be ordered intravenous (IV) injection daily for the first two to three days and after that reduced to 50 mg/kg daily up to six weeks.
4. Moderate to severe PQ poisoning patients were ordered Glucocorticoid agents such as methylprednisolone one gram daily IV for three days then dexamethasone 8 mg three times a day (IV/oral) for 14 days. If PaO2 was <60 mmHg or patient is deteriorating without other explainable reason, pulse therapy with methylprednisolone gram daily IV could repeat for 3 days.
5. Moderate to severe PQ poisoning patients were recommended by15 milligrams per kilograms per day (maximum one gram) of cyclophosphamide daily during two days with mesna 15 mg/kg for four days. Drugs adjustment might be needed for patient with renal or liver impairment developed. Early administration of cyclophosphamide with mesna may be recommended at least 2-3 hours after PQ exposure for a short period on the initial 3-4 days.
6. Antibiotics must be given in prolonged use of immunosuppressant agents or in the presence of fever.

Step 5 (Discharge)

When the kidney and liver function returned to normal level, and the patient was stable, he would be discharged considering follow-up every week for evaluating lung fibrosis until six weeks. It is better that examination and follow-up is done by an Internist or lung specialist.

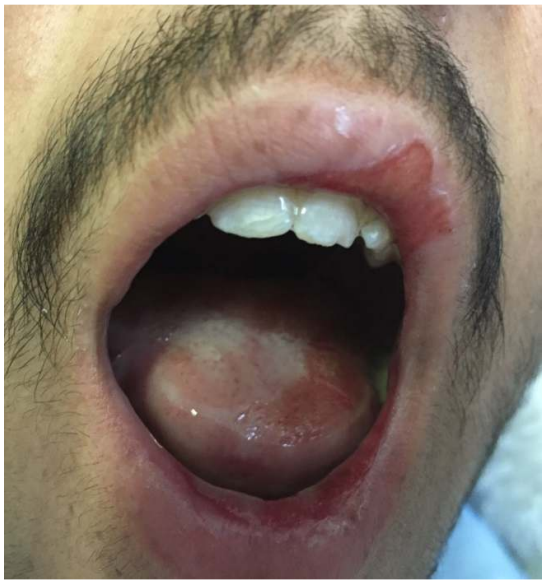

Fig. 1. Paraquat tongue, one week after ingestion with extensive ulceration

4. DISCUSSION

PQ is an herbicide of toxicological importance. Fatality rate of PQ poisoning is great without signification with respect to the patient characteristics [6]. PQ ingestion as suicidal attempt is common in Isfahan. It may be due to wide spread availability and relatively low cost [6]. It seems challenging for devising a treatment protocol in PQ intoxication. Most of the information used for its treatments is based on animal and case report researches, and there are a few clinical trial studies in this scope. It should be noted that our proposed guideline is not idealized for every situation and the clinical judgment of the treating physician should be based on the available medication resources and patient's condition. Moreover, this is an in

hospital management and does not include recommendations of pre-hospital care. Initial emergency assessment, stabilizing and evaluation ofPQ poisoned case are done on admitted the same as other emergency patients. Valuable physiologic clues can help to finding toxicological etiology and severity of an illness and necessity to supportive treatment. The next approach is involved closer examination of the risks and benefits of gastrointestinal emptying interventions. It is not recommend in esophagus tissue damages caused by corrosive effect of PQ [39].

The efficacy of extra-corporeal elimination of PQ by HP is higher than HD but HP in clearing serum PQ depends on the blood flow, function of the HP cartridge and plasma levels when renal function is normal [40]. Damage of kidney is observed at the early stage of severe PQ intoxication. Although the benefits of this will be very limited, however, HD could be considered in patients who suffer of symptomatic acute renal failure and when there is no availability of HP.

Human studies of antioxidant agents as potential antidotes for PQ poisoning have either been absent or small and uncontrolled. There were not established indications and complication s as the optimal dose of them [11].

In the rats; treatment with a-tocopherol liposomes alleviated the progression of PQ - induced lung damage as decrease lipid peroxidation [41]. In a human study, some patients treated with vitamin E (200–4000 mg/ day) [42-44].

Ascorbic acid is an antioxidant to the ability of scavenging free radicals resulted from PQ stress, including superoxide anions, hydroxyl radicals and aqueous peroxyl radicals [45-47]. Although, the safety issue of high doses of vitamin C treatment has not been proved in human, but its use caused normalization of the biochemical and histological parameters in animals [45-48]. However, several researches shown that vitamin C may be useful in the treatment against PQ toxicity [49-51].

Vitamin C is infused150 mg/hour.Intravenous injection rates are100-150 mg per hour in 100 ml distilled water or dexstrose water 5%.In human studies 50 mg/kg has been administered and maximum total dose of it is considered as 3000 mg per day in some studies [51].

NAC 150-300 mg/kg administered IV daily similar to other studies for the first two to three days and after that reduced to 50 mg/kg daily up to six weeks.

N-Acetylcysteine is a low-molecular-weight thiol-containing antioxidant with free radical-scavenging properties, ratelimitingin the synthesis of glutathione in alveolar type II pneumocytes and reduction of paraquat-induced apoptosis [52,53]. NAC is able to limit inflammatory processes in lung [54], and has a beneficial effect on the mitochondrial membrane potential of PQ-challenged cells [55]. Most of these antioxidants have low plasma membrane permeability. They are sustained by the ex-tensive supply of electrons and oxygen in the lungs, therefore, optimal dose of anti-oxidants should be administered without cessation. However, it is difficult to administer high dose of antioxidants for several days without cessation. Although oral NAC is recommended typically 600–1200 mg pills up to 3 times daily for 12 week period in adult patients of normal body weight in the absence of enzyme-inducing drugs, for PQ poisoned patients who has erosion in GI and nausea and vomiting we recommend to administer IV NAC [56].

PQ leads to an acute inflammatory response that follows by lung fibrosis and death. The most widely surveys treatment uses cyclophosphamide, MESNA, methylprednisolone and dexamethasone [27,57-59]. Although, immunosuppressive therapy are making patients more prone to infection in the long term, but these agents might reduce deaths among paraquat poisoned patients [60]. Glucocorticoid agents such as dexamethasone and methylprednisolone have been shown to increase the expression of P-glycoprotein and other transporters. They also reduce lipid peroxidation. It ameliorates the histological and biochemical changes induced by PQ in rats [60,61]. Immunosuppressant agents are practiced as reduce acute inflammatory response. Because the most pathologic changes are completed within the first few days of intoxi-cation, its administration should do as soon as possible after PQ exposure and continue for 2 days. Based on Li et al. [60] research, cyclophosphamide with glucocorticoid in addition to standard care had a lower risk of mortality at final follow-up. And there may be a beneficial medication for patients with lung fibrosis due to PQ intoxication.

5. CONCLUSIONS

Based on animal surveys and limited human data, NAC, vitamin C and E and immunosuppressant agents may have hopeful mechanisms to counter the pathophysiological effects following PQ intoxication. However, management and treatment are needed to guide the choice of dosages, duration and combinations. On the other hand, this plan may be suitable considering available equipment in our hospital. This guideline should be evaluated in terms of clinical studies.

CONSENT

It is not applicable (since the patient died we couldn't get informed consent. Also the picture of the patient is not recognizable).

ETHICAL APPROVAL

The research protocol of this study has been approved by Clinical Toxicology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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