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Original Article

Clinical features and prognosis of paraquat poisoning: a review of 41 cases

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Abstract: Purpose: Paraquat is a contact herbicide which is highly toxic to human. Deliberate self-poisoning with paraquat continues to be a major public health concern in many developing countries. This study aimed to evaluate the data on cases of acute paraquat poisoning and to compare different variables between survivors and non-survivors. Methods: In this cross sectional study, medical records of all paraquat intoxicated patients were reviewed at Taleghani hospital of Urmia, Iran, from 2007 to 2013, retrospectively. Demographics, clinical features and laboratory findings were evaluated. The variables compared between survivors and non-survivors were the amount of paraquat ingested, occurrence of vomiting after ingestion, time and place of hospital admission, length of hospital stay, leukocytosis, serum creatinine level and the outcomes. Results: A total of 41 patients were evaluated. The mean ± standard deviation of patients' age were 31.6±16.9 years. The Length of hospital stay was 5.75±4.6 days. Most poisonings occurred in spring and summer. The in-hospital fatality rate was 46.3%. Statistically significant associations were found between the outcome of patients and the amount ingested (P=0.001), vomiting (P=0.004), early need to intensive cares (P=0.009), leukocytosis (P=0.001), serum creatinine levels (P=0.001), manifestations of acute hepatic (P<0.001) and respiratory failure (P=0.007). Conclusion: Ingestion of more than 30 ml, prompt vomiting, early need to intensive cares, leukocytosis, and multi-organ failures are major determinants for fatal outcome of paraquat poisoning. It may be useful to educate health professionals and the general population about the serious consequences of exposure to paraquat.

Keywords: Paraquat poisoning, suicide, deliberate self-harm, fatal outcome, herbicides, pesticides, toxicology

Introduction

Paraquat (1, 1'-dimethyl-4, 4'-bipyridinium dichloride) is a fast-acting and non-selective contact herbicide widely used in agricultural and horticultural industries around the world [1-4]. Today, it is the world's second largest selling weed-killer in over 100 countries [2, 5].

Paraquat is highly toxic for human and most animals [1, 2]. Ingestion of paraquat is the most common route of poisoning [1, 3, 6], however poisoning through other routes including dermal or mucus contact [7, 8], inhalation [9, 10] or injection [11-15] have also been reported.

As little as a teaspoon of concentrated paraquat can result in death [16]. In an adult human, estimated lethal dose is about 30 mg/kg [17] or 3-6 g of paraquat ion [3, 6] which is equivalent to 10 to 20 mL of 20% solution.

Paraquat is rapidly but incompletely absorbed and then largely eliminated unchanged in urine within 12-24 h. Clinical features are mainly due to generation of intracellular reactive oxygen species which cause cellular damage via lipid peroxidation, activation of nuclear factor kappa B, mitochondrial damage and apoptosis in many organs [18]. Paraquat is actively taken up against a concentration gradient into lung tissue leading to pneumonitis and lung fibrosis [18]. Paraquat also damages the heart, kidneys, liver, adrenal glands, central nervous system, muscles and spleen causing multiple organ failure [16, 18, 19]. Clinical reports associated paraquat poisoning with acute lung injury, pulmonary hypertension, leukocytosis, metabolic acidosis, enlarged heart, acute kidney

injury, generalized edema and increased level of amylase, glucose and creatinine [16]. Until now, there has been no effective antidote.

Among all those pesticides used as suicide agents, paraquat plays a major role. The case fatality is very high in all centers despite large variations in treatment [18, 20] and the mortality varies between 50% and 90%, but in cases of intentional self-poisoning with concentrated formulations, mortality approaches 100% [18].

The general perception is that the use of paraquat for deliberate self-harm or suicide is mainly a problem in developing countries, but, a recent study reported that in the United States of America, it was the cause for more deaths than any other pesticide in 2008 [16]. Because of its high toxicity, the European Union withdrew paraquat from its market in July 2007 [2, 18, 21].

In Iran, paraquat is the first registered herbicide at 22 Dec 1968 by Plant Protection Organization and has been marketed as 20% aqueous solution of dichloride salt (Gramoxone, ICI) [22]. We found a few published studies about paraquat poisoning in Iran. Sabzghabaee et al reported 29 cases of paraquat poisoning during a five-year period (2002-2006) in Isfahan province, Iran, with the fatality rate of 55.2% [23]. They concluded that a large amount of ingested paraquat, vomiting and age may be important variables in association with outcome of paraquat poisoning [24]. Amiri et al studied 52 cases of paraquat poisoning in Lorestan province, Iran, and reported 71.1% fatality rate [25]. They also concluded that the amount of ingested paraquat and time interval between poisoning to arrival at hospital were major determinants of lethality [25]. Afzali et al studied the effectiveness of immunosuppression on 45 paraquat intoxicated patients in a case-control study during a 2-year period in Hamadan province, Iran, and concluded that pulse therapy with cyclophosphamide and methylprednisolone may be effective in preventing respiratory failure and reducing mortality in patients with moderate to severe paraquat poisoning [19]. However, the exact number of morbidity and mortality of paraquat poisoning in Iran is not clear.

Given the importance of the topic, current study aims at describing the demographic characteristics, clinical features, laboratory findings and outcomes of paraquat poisoning during a seven-year period in West Azerbaijan province of Iran.

Materials and methods

In this retrospective descriptive analytical study, all patients admitted to the poisoning treatment center of Ayatollah Taleghani Teaching Hospital of Urmia, West Azerbaijan, Iran, for alleged paraquat poisoning were evaluated from 1st of January 2007 to 31st of December 2013. No personal identification data were recorded and all information obtained from the medical records was kept confidential. All tools and methods used in this research project were approved by the Ethics Committee of Research and Technology Deputy of Urmia University of Medical Sciences.

Urmia is the center of West Azerbaijan Province, north-west Iran. According to last national census (2012), the population of Urmia and the province was 963,738 and 3,080,576 (about 4.1% of country population) people, respectively. Ayatollah Taleghani Teaching Hospital is the second largest local public hospital. Poisoning Treatment Center of the hospital is the only referral center for poisoned patients in the province to which almost all paraquat intoxicated patients were referred.

The study included patients with the ages above 14 years old who were presented to the Emergency Department with paraquat poisoning during the study period. This includes patients who were self-admitted or with witness account of paraquat exposure (ingestion, inhalational, mucosal or skin contact).

Data was obtained manually from the patient's medical records. The information recorded includes age, gender, marital status, living place, the route of intoxication, amount ingested, admission date and place, the length of hospital stay, symptoms and signs, laboratory findings, treatment received and outcomes.

The data were analyzed using SPSS version 20. Descriptive statistics were presented as mean ± standard deviation (SD) and percentage, where appropriate, to summarize the demographic characteristics, clinical features and outcomes of the cases. The variables were also compared between survivors and non-survi-

Table 1. Demographic characteristics of the paraquat-intoxicated patients (N=41)

Characteristics	Number (%) of patients
Gender	
Male	23 (56.1)
Female	18 (43.9)
Age (years)	
14-20	10 (24.4)
21-30	19 (46.3)
31-40	3 (7.3)
41-50	1 (2.4)
51-60	4 (9.8)
≥ 60	4 (9.8)
Median	25
Range	16-75
Season of admission	
Spring	16 (39.0)
Summer	13 (31.7)
Autumn	7 (17.1)
Winter	5 (12.2)
Living area	
Rural	23 (56.1)
Urban	18 (43.9)
Marital status	
Married	26 (63.4)
Single	15 (36.6)

vors. The *t* test was used to investigate the differences of quantitative variables. The relationships between categorical variables and the outcomes were evaluated using Chi square test where appropriate. In all cases, a confidence interval of 95% and a significance level of 5% ($P<0.05$) were considered.

Results

The medical records of 41 patients were reviewed in this study. The majority were male (n=23, 56.1%). Male to female ratio was 1.28. The mean ± standard deviation (SD) of patients' age and length of hospital stay were 31.6±16.9 years and 5.75±4.6 days, respectively. The in-hospital fatality rate was 46.4% (n=19) including 56.5% (n=13) for males and 33.3% (n=6) for females. **Table 1** shows some demographic characteristics of the studied patients.

All patients ingested the paraquat orally and other routes of poisoning were not observed. Ingestion of paraquat was for deliberate self-harm or suicide in 85.4% (n=35), accidental in 9.8% (n=4) and unknown in 4.9% (n=2). The primary diagnosis was paraquat poisoning in 92.7% (n=38), organophosphate poisoning in 4.8% (n=2) and upper gastrointestinal bleeding in 2.4% (n=1). Clinical characteristics and outcomes are showed in **Table 2**.

The amount of ingested paraquat was stated by patients as mouthful, cap of container and all or part of a mug or cup. We considered the volume of a mouthful equal to 30 ml, a normal mug and cup equal to 250 and 150 ml, respectively. The volume of a sample of one-liter paraquat container cap was measured as 25 ml. In existence of reminder of ingested poison, we estimated the ingested volume by direct measuring of residual volume and asking for recent or previous use of poison. The mean ± SD of ingested paraquat was 149.3±225.4 ml (n=36). This amount was 193.18±274 ml for males (n=22) and 80.4±84.6 ml for females (n=14). The observed difference between genders was not statistically significant (P=0.08). For survived and non-survived patients, the average amount of ingested paraquat was 23.4 ml (SD=22.3, Min=5, Max=100, N=19) and 290 ml (SD=266, Min=30, Max=1000, N=17), respectively. The difference was statistically significant (P=0.001). After sorting of the ingested amount in ascending order, further analysis showed that all patients who ingested fewer than 25 ml (n=14) were survived while all patients who ingested more than 150 ml (n=12) deceased. Half of the patients who ingested 30-150 ml (n=10), were survived.

The main symptoms and signs of studied patients include nausea (53.7%); vomiting (43.9%); epigastric pain (36.6%); mucosal lesions of oral cavity and pharynx (85.4%); loss of consciousness as mild to moderate lethargy (9.8%); and fever (9.8%).

Leukocytosis was seen in 41.7% of patients (n=17). The peak of leukocytosis in survived patients was on the first day but, in non-survived patients, the peak occurred on the 2nd or 3rd days after admission and the leukocytosis continued until death. There was a statistically significant relationship between leukocytosis and death ($P<0.001$). Anemia was seen in 22% of patients (5 men and 4 women). No obvious thrombocytopenia was seen.

Table 2. Clinical characteristics and outcome of paraquat intoxicated patients (N=41)

Characteristics	Number (%) of patients		*P* value
	Survivor	Non-survivor	
Admission service			0.009
Ward	20 (69)	9 (31)	
ICU	1 (14.3)	6 (85.7)	
First ward then ICU	1 (20)	4 (80)	
Amount of ingested paraquat (mL)	23.4±22.3	290±266	0.001
Duration of hospital stay (days)	7.25±4.35	4.01±4.43	0.024
Vomiting			0.004
Yes	5 (27.8)	13 (72.2)	
No	17 (73.9)	6 (26.1)	
Loss of consciousness			0.038
No	22 (59.5)	15 (40.5)	
Mild to moderate lethargy	0 (0)	4 (100)	
Shock			0.016
Yes	0 (0)	5 (100)	
No	22 (61.1)	14 (38.9)	
Leukocytosis			<0.001
Yes	3 (17.6)	14 (82.4)	
No	19 (79.2)	5 (20.8)	
Increased serum creatinine			0.001
Yes	8 (32)	17 (68)	
No	14 (87.5)	2 (12.5)	
Respiratory failure			0.007
Yes	0 (0)	16 (100)	
No	22 (88)	3 (12)	
Acute hepatitis			<0.001
Yes	1 (7.7)	12 (92.3)	
No	21 (75)	7 (25)	

Acute hepatitis was seen in 31.7% (n=13) of patients. Mean ± SD of alanine transaminase (ALT) and aspartate transaminase (AST) in these patients were 244.8±219.2 and 181.8±118.1 IU, respectively. Increased serum bilirubin was seen in 22% of patients (n=9). The mean ± SD of total and direct serum bilirubin in these patients were 6.5±91 mg/dl and 4.1±5.2 mg/dl, respectively. All patients with elevated bilirubin died. On the contrary, no survived patients had increased serum bilirubin.

Significant increases in serum creatinine (Cr) was seen in 61% of patients (n=25). The mean ± SD of Cr for these patients was 3.9±2.1 mg/dl (Min=1.6, Max=8.8). There was a statistically significant relationship between increased serum Cr and the outcome of patients (P=0.001).

Endoscopic examination had been performed for 48.8% of patients (n=20) and different degrees of inflammations and/or ulcers were reported alongside the upper gastrointestinal tract. Only 26.3% (n=5) of non-survived patients were undergone endoscopy from which all have severe degrees of ulcerative lesions along the upper gastrointestinal tract. Bad situation of other non-survived patients did not permit for endoscopic examination.

Therapeutic interventions included nasogastric tube insertion, gastric lavage and administration of activated charcoal and sorbitol were performed for all patients. Other interventions were intravenous (IV) metoclopramide for 41.5% of patients, peptic ulcer prophylaxis (by IV ranitidine, cimetidine or pantoprazole) (90.2%), IV sodium bicarbonate (73.2%), immunosuppression using IV glucocorticoids (hydrocortisone, dexamethasone or methylprednisolone) (53.7%) or cyclophosphamide (22%), N-acetyl cysteine (14.6%), silymarin (17.1%), vasopressor agents (dopamine and/or dobutamine) (12.2%), intra-tracheal intubation (39%) and mechanical ventilation (22%).

Hemodialysis had been performed for 92.7% of patients (n=38). The mean ± SD of interval between hospital admission and start of hemodialysis was 6.73±12.7 hours. The average frequency of hemodialysis was 1.46±0.84 times. No significant relationship was found between outcome and hemodialysis (P=0.09), or its frequency (P=0.12) or starting time (P=0.88).

Respiratory, renal and hepatic failure were clinically observed in 39% (n=16), 61% (n=25) and 31.7% (n=13) of patients. From two non-survived cases without increased Cr levels, one man ingested 500 ml and another woman swallowed 200 ml of paraquat who both died 8 and 12 hours after admission, respectively, before the development of acute kidney injury.

The most common causes of death were multi-organ failure in 57.9% (n=11) followed by respi-

ratory failure (31.6%, n=6), cardiogenic shock (2.4%, n=1) and hemorrhage (2.4%, n=1). The latter case was a man who was under heparin therapy for mitral valve replacement. The burial permits of 15.8% (n=3) of died persons were issued by clinical toxicologists and other cases were referred to local legal medicine office.

Discussion

From the cases reviewed, it was found that many of paraquat intoxicated patients were from the age group of 21 to 30 years old (46.3%) with median age of 25 years. These are the productive age group in the population. Their loss can be devastating to the family as well as the society. More in-depth study is necessary to look into the reasons for this observation.

In our study, the majority of exposures (89.7%) were intentional, mainly from deliberate self-harm. The previous study in Lorestan, Iran, by Amiri et al (2008) found that attempted suicide accounted for 76.9% of poisonings [25]. Sabzghabaee et al (2010) also reported 100% of paraquat poisoning in a series of 29 patients in Isfahan, Iran, were suicidal attempts [23].

Seasonal variation of paraquat poisoning is noticeable, more than 70% of our cases occurred in spring or summer. This was similar to the study of Amiri et al [25] who reported more prevalence in the summer.

Most of our cases were from north of the province, where farmers grow sunflowers in large quantities and use paraquat for eliminating weeds. Based on experts opinion in local office of Plant Protection Organization, the amount of paraquat used in one city (Khoy) are more than the total use of other cities in the province. Some studies suggest that the easy access to a potent substance, in this case paraquat, increases the number of suicides and may result in death when in fact there was no definite intention on the part of the victims to commit suicide [16].

The severity and outcome of paraquat poisoning are determined primarily by the amount ingested. However, in most cases, it is difficult to determine accurately the amount. In our study, less than 25 ml associated with good prognosis. Some literatures suggested 10 to 20 mL of 20% solution can result in death [19]. Amiri et al concluded 20 ml as cut off point for fatality [25].

There was also statistical significance between admission service and outcome (P=0.009) so, ill patients who need critical cares on admission and transferred to ICU have high mortality rate (see **Table 2**).

In our review, 4 patients had mild degrees of loss of consciousness on admission and all deceased. Paraquat intoxicated patients generally maintain a normal level of consciousness. Any impairment usually indicates either co-ingestion of other agents or severe toxicity resulting in altered consciousness from hypoxia, hypotension and severe acidosis [18].

There was a significant relationship between the patients' outcome and vomiting in our study so early presentation of vomiting was associated with poor prognosis. Sabzghabaee et al had found a weak relationship [23]. Some studies have evaluated the role of the prevention of paraquat absorption by using a potent emetic in paraquat formulations; however, the efficacy of these measures on paraquat fatality has not been definitively demonstrated, which may be due to the large amount of paraquat ingested [23].

Important variables for the high fatality rate of paraquat intoxication in our study were a large amount of ingested volume, prompt vomiting, loss of consciousness, need to ICU admission on entrance, leukocytosis, initial appearance of respiratory, hepatic or renal failure, development of sever hypotension or cardiogenic shock and need the infusion of vasopressor agents.

Here, hemodialysis is used for the majority of our patients. Although, no significant relationship was found between hemodialysis and clinical outcome, overall in-hospital fatality in our center was 46.4% which was less than very high case fatalities (50%-90%) reported in other studies [18, 26]. Whether our lower fatality rate associates with performing hemodialysis for the most cases, further investigation could show the effectiveness of hemodialysis on outcome of paraquat poisoning.

The main limitation of our study was the inability to test the level of serum or urine paraquat.

A semi-quantitative test using bicarbonate and sodium dithionite can be used as a bedside test to confirm systemic paraquat toxicity [16, 18, 19]. Other limitations were lack of data for time interval between ingestion of paraquat and going to the hospital, unavailability of fuller earth, bentonite and hemoperfusion facilities in our center, and above all the absence of an exact protocol or constant approach for management of paraquat intoxicated patients.

Paraquat poisoning is still a concern in developing countries. It may be useful to educate public health professionals and the general population about the serious consequences of exposure to this toxic agent. Paraquat poisoning is still no cure. More research is needed to determine the effectiveness of various treatments. Due to the low number of cases of paraquat poisoning, we would encourage anyone seeing a substantial number of paraquat poisonings to adopt a consistent strategy for a number of patients, to measure the paraquat concentration (the best prognostic predictor) and to report their outcomes.

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Disclosure of conflict of interest

None.

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