ORIGINAL ARTICLE

Mortality Analysis of Patients with Paraquat Poisoning Treated at Two University Hospitals in Shiraz, Iran

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Abstract

Background: Poisoning with paraquat (PQ) is highly fatal. In this study; demographic and clinical characteristics of a series of patients with acute PQ poisoning treated at two university hospitals in Shiraz, Iran are presented and predictive factors for mortality are analyzed.
Methods: This was an analytical cross-sectional study on consecutive PQ poisoned patients admitted to Shoushtari and Ali Asghar hospitals in Shiraz, Iran during 21st March 2012 to 20th March 2013. To find out predictive factors for mortality, independent variables were compared between death and survival using Fisher's exact test. To determine the factors that had the strongest impact on mortality, logistic regression analysis was done.
Results: Fifty-two patients (73.1% men) were included with mean age of 28.2 ± 10.3 years. The most common clinical findings were nausea and vomiting (88.5%), pharyngeal congestion (82.7%), epigastric pain (80.8%), increased creatinine (57.7%), increased liver enzymes (53.8%) and metabolic acidosis (53.8%). The volume of poison ingested was significantly higher in deceased compared to survived patients ($P < 0.001$). Death was significantly higher in patients with pharyngeal congestion ($P = 0.001$), respiratory distress ($P < 0.001$), loss of consciousness ($P = 0.025$), increased creatinine ($P < 0.001$), increased liver enzymes ($P < 0.001$), metabolic acidosis ($P < 0.001$), increased bilirubin ($P < 0.001$), respiratory acidosis ($P = 0.001$), increased INR ($P = 0.023$), suicidal intention ($P < 0.001$), and oral exposure ($P = 0.047$). After putting these factors to logistic regression model, only respiratory distress, increased bilirubin, increased liver enzymes and increased creatinine continued to be significantly associated with mortality.
Conlcusion: PQ poisoning is associated with high mortality requiring an immediate assessment of patients and prediction of prognosis. Renal and hepatic failure in addition to respiratory distress can be the strongest risk factors for poor prognosis in acute PQ poisoning.

Keywords: Mortality; Paraquat; Pesticides; Poisoning; Risk Factors

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INTRODUCTION

Poisoning with paraquat (PQ) is one of the most fatal poisoning cases which clinicians would face in an emergency department (1). PQ is a broad spectrum herbicide with low price, and thus it has been widely used in developing countries for agricultural purposes (2). It is available as concentrated liquid or granules which can be resolved in water or can be distributed as aerosols into the air (3). The mechanisms of action of this substance include: generation of the superoxide anion leading to formation of highly toxic reactive oxygen radicals, oxidation of the cellular nicotinamide adenine dinucleotide phosphate (NAPDH), and lipid peroxidation (4). Therefore, PQ is able to produce highly toxic radicals which can attack unsaturated fatty acids of cell membrane and consequently destroy the cell membrane structure (4,5). In PQ poisoning, most system organs including respiratory, digestive, cardiovascular, central nervous and integumentary systems can be severely affected depending on the amount of the poison ingested (6).

PQ poisoning corresponds to ingestion of over 20 mg/kg PQ or serum PQ levels of greater than 0.2μg/mL within 24 hours, while serum levels of more than 0.1 mg/mL within 48 hours are associated with fatal outcomes (5,7). Immediate treatment is a determining factor on survival of PQ poisoned patients (6). Airway protection, fluid therapy, decontamination techniques, hemodialysis and steroid therapy are the principal treatments for PQ poisoning. Nevertheless, there is still no specific antidote against PQ poisoning (6,8). Approximately half of PQ poisoned patients are vulnerable to death which is closely associated with the amount of poison ingested and some other factors (6,9). Poisoning with PQ is an infrequent but a life-threatening emergency in Iran (10,11). Hence, it is crucial for clinicians to evaluate the prognosis of the patients for planning a better treatment strategy and allocating intensive care unit (ICU) beds to patients with severer conditions. In this study;

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demographic and clinical features of a series of patients with acute PQ poisoning treated at two university hospitals in Shiraz, Iran are presented and predictive factors for mortality are analyzed.

METHODS

Patients and setting

This was an analytical cross-sectional study on consecutive PQ poisoned patients admitted to Shoushtari and Ali-Asghar hospitals in Shiraz, Iran during 21st March 2012 to 20th March 2013. These two hospitals are referral medical settings for admission of poisoning cases in Fars province, southwest Iran. They provide emergency care, inpatient care and intensive care services for all types of poisoning.

Data collection and ethics

Data including demographic features and clinical manifestations of, treatments administered to and final outcomes (death or survival) of patients were recorded into predesigned checklists. Based on history taken from patients or their relatives, time of poisoning, route of exposure and the volume of poison consumed were also recorded in checklist. The study was approved by the ethics committee of Shiraz University of Medical Sciences. The clinical details were entered into the checklists by maintaining the confidentiality of the patients' information.

Statistical analysis

Collected data were entered into statistical package for social sciences (SPSS) software (SPSS Inc., Chicago, USA). Kolmogorov-Smirnov test was used to assess the normality of data. For comparison of means difference between two groups, independent samples T-test was used if the data were normally distributed and Man-Whitney U test was used for non-normal variables. To find out predictive factors for mortality, independent variables were compared between death and survival using Fisher's exact test. The risk values of potential factors for mortality are reported with odds ratio (OR). Moreover, to determine the factors that had the strongest impact on mortality, logistic regression analysis was done. In this study, probability values of less than 0.05 were considered statistically significant.

RESULTS

Demographic features and circumstances of poisoning

During the study period, 6584 patients with different types of poisoning were hospitalized in the two hospitals, which among them, 52 patients were poisoned with PQ (0.8%).

Of 52 PQ poisoned patients, 73.1% were men. Mean age of the PQ poisoned patients was 28.2 ± 10.3 (range: 15 - 60) years. Most patients were 20 to 30 years old (Figure 1). Intention of poisoning was suicidal attempt in most patients (73.1%). PQ was taken orally in most cases (93.2%). Median time interval between poisoning and arrival in hospital was 4 (range: 0.5-96) hours. The volume of poison ingested by the patients ranged from 5 to 300 mL. Regarding gender distribution of patients, there was no significant difference between mean age of men and women (P = 0.161); however, poisoning with suicidal purposes was significantly more common in men (P = 0.035) (Table 1).

Clinical manifestations, treatments and outcomes

The most common clinical manifestations of patients were nausea and vomiting (88.5%), pharyngeal congestion (82.7%) and epigastric pain (80.8%). The most common laboratory findings were increased creatinine (57.7%),

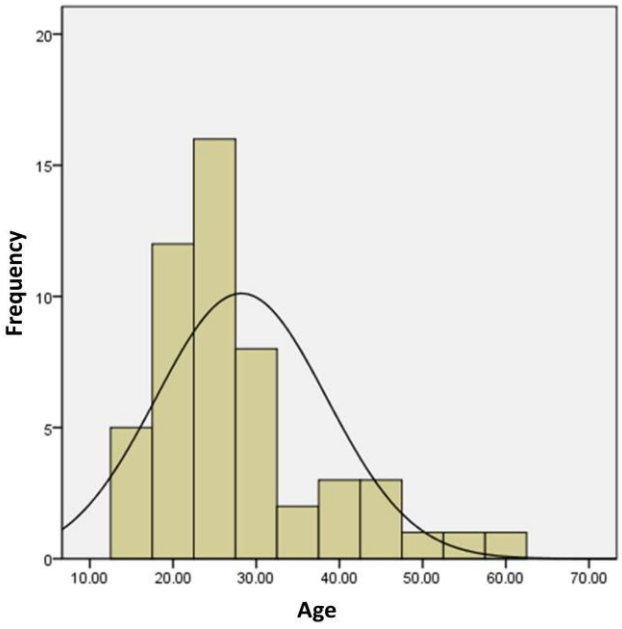

Figure 1. Age distribution of patients

Table 1. Analysis of patients' age and intention of poisoning according to gender

	Gender		P value
	Male (n = 38)	Female (n = 14)	
Age (year)*	29.1±11.4	25.7±5.7	0.161*
Intention of poisoning**			
Suicidal	31 (81.6)	7 (50.0)	0.035**
Accidental	7 (18.4)	7 (50.0)	

* Presented with mean ± SD, and analyzed with independent samples t-test

** Presented with number (%), and analyzed with Fisher's exact test

increased liver enzymes (53.8%), metabolic acidosis (53.8%) and increased bilirubin (50.0%). Treatments delivered to patients included: active charcoal + sorbitol for 86.5%, antacid + antiemetic for 96.3%, steroid therapy (intravenous dexamethasone 8mg q6-8 hours until clinical improvement + infusion of methylprednisolone 500 mg in 6 hours for 3days) for 86.5%, N-acetyl cysteine (140 mg/kg bolus + 70 mg/kg q4-6 hours) for 82.7%, vitamin C (1 g q12 hours) for 75%, vitamin E (400,000 IU q24 hours) for 75% and hemodialysis for 61.5% of patients. Twenty-seven patients (51.9%) died, 24 patients could be discharged without any sequel and one patient discharged with minor gastric irritation.

Mortality analysis

By comparing deceased and survived patients, it was found that the volume of poison ingested was significantly higher in deceased patients ($P < 0.001$), while patients' age and the time elapsed from poisoning to arrival in hospital did not differ significantly between death and survival (Table 2).

For identification of the value of potential factors for prognosis of PQ poisoning, demographic and clinical features of patients, intention of poisoning and route of exposure were compared between deceased and survived cases (Table 3). As can be seen, death was significantly higher in patients with pharyngeal congestion ($P = 0.001$), respiratory distress ($P < 0.001$), loss of consciousness ($P = 0.025$), increased creatinine ($P < 0.001$), increased liver enzymes ($P < 0.001$), metabolic acidosis ($P < 0.001$), increased bilirubin ($P < 0.001$), respiratory acidosis ($P = 0.001$), increased INR ($P = 0.023$), suicidal intention ($P < 0.001$), and oral exposure ($P = 0.047$). After putting these factors to logistic regression model, only respiratory distress ($P < 0.001$), increased bilirubin ($P < 0.001$), increased liver enzymes ($P < 0.001$) and increased creatinine ($P < 0.001$) continued to be significantly associated with mortality. In this sense, it can be said that patients with increased liver enzymes had 299.0 fold risk, with respiratory distress had 32.85 fold risk, with increased bilirubin had 26.0 fold risk, and with increased creatinine had 10.0 fold risk for poor prognosis (death) (Table 3).

DISCUSSION

In this study, a case series of patients with acute PQ poisoning in north-west Iran was presented with 52% mortality. This kind of poisoning has been reported to be associated with high fatality in different parts of the world ranging from 35 to 62% consistent with our findings (12-18). The very high case fatality rate of PQ poisoning is due to both its inherent toxicity and the lack of effective treatment and specific antidote (6). Management of this poisoning mainly relies upon supportive treatments and extracorporeal removal techniques such as hemoperfusion and hemodialysis for severe patients (2,6,19). Nevertheless, the outcome of patients is basically depended on the severity of poisoning and the quickness of the medical care provided for them (6,7,15). Therefore, a clinician at the emergency department essentially needs to appraise the prognosis of a PQ poisoned patient to decide the most appropriate treatment and to know to which patient the ICU bed should be allocated.

In this study, through logistic regression analysis we found that increased liver enzymes, increased bilirubin, increased creatinine and respiratory distress were the strongest risk factors for poor prognosis in PQ poisoning. Using logistic regression, Hong et al similarly showed that patients with renal or hepatic dysfunction, or metabolic acidosis had significant risks of the fatality (16). Lee et al found renal or hepatic failure and metabolic acidosis as poor predictive factors for PQ poisoning resembling the findings of Hong et al and the present study (17). Liu et al likewise identified renal dysfunction and metabolic acidosis as important factors for the prognosis of PQ poisoning (18). Among the clinical variables that were significantly associated with mortality in the present study, metabolic acidosis was one the factors that acquired a very high OR, though it was excluded after controlling in logistic regression analysis. Acid-base imbalances following PQ poisoning correspond to multi-organ failures (6,16,20). PQ is capable of affecting all end-organs with high blood flow including liver, kidney, spleen, adrenal glands and lungs. Lungs can be considered as the most common affected organs in severe PQ poisoning (6,7). Pulmonary tissue is damaged by the mechanism of redox cycling showing itself with respiratory distress at early stages and with pulmonary fibrosis within 10 to 15 days of ingestion (6,21). In the present study, we found respiratory distress as one of the strongest factors for mortality. This replicates the findings of the studies by Agrawal et al, Lee et al and Sandhu et al which ascertained respiratory distress as major cause of death in PQ poisoning (1,14,17). By and large, taking these clinical and laboratory findings on admission into account can provide practical and useful information for the clinicians to have a better insight on the severity of PQ poisoning and an improved foresight on prognosis of the patients.

Compared to accidental situations, suicidal poisonings are associated with ingestion of higher amounts of poison resulting

Table 2. Analysis of outcome according to patients' age, time interval between poisoning and arrival in hospital, and volume of paraquat ingested

	Outcome; n (%)		P value
	Death	Survival	
Age (year)*	28.9 ± 10.9	27.5 ± 9.7	0.625
Time interval between poisoning and arrival in hospital (hour)**	4 (1-96)	3 (0.5-36)	0.289
Volume of paraquat ingested (mL)**	50 (15-300)	10 (5-50)	< 0.001

* Presented with mean ± SD, and analyzed with independent samples t-test

** Presented with median (range), and analyzed with Mann Whitney U test

Table 3. Analysis of outcome in patients with paraquat poisoning

	Total; n	Outcome; n (%)		Odds ratio (95% confidence interval)	P value*
		Death (n = 27)	Survival (n = 25)		
Gender					
Male	38	20 (74.1)	18 (72.0)	1.11 (0.32-3.78)**	~ 1
Female	14	7 (25.9)	7 (28.0)		
Clinical manifestations					
Nausea and vomiting	46	26 (96.3)	20 (80.0)	6.50 (0.70-60.13)	0.094
Pharyngeal congestion	43	27 (100)	16 (64.0)	2.68 (1.82-3.96)	0.001
Epigastric pain	42	24 (88.9)	18 (72.0)	3.11 (0.71-13.72)	0.167
Respiratory distress	22	20 (74.1)	2 (8.0)	32.85 (6.11-176.62)	<0.001
Loss of consciousness	9	8 (29.6)	1 (4.0)	10.11 (1.16-87.99)	0.025
Seizure (n = 1)		1 (3.7)	0 (0.0)	1.96 (1.50-2.56)	~ 1
Laboratory investigations					
Increased creatinine[1]	30	27 (100.0)	3 (12.0)	10.0 (3.41-29.41)	<0.001
Increased liver enzymes[2]	28	26 (96.3)	2 (8.0)	299.0 (25.41-3517.80)	<0.001
Metabolic acidosis	28	24 (88.9)	4 (16.0)	42.0 (8.41-209.57)	<0.001
Increased bilirubin[3]	26	26 (96.3)	0 (0.0)	26.0 (3.80-177.68)	<0.001
Leukocytosis[4]	16	11 (40.7)	5 (20.0)	2.75 (0.79-9.54)	0.138
Respiratory acidosis	13	12 (44.4)	1 (4.0)	19.20 (2.26-163.11)	0.001
Respiratory alkalosis	10	6 (60.0)	4 (40.0)	1.50 (0.37- 6.09)	0.729
Increased INR[5]	6	6 (22.2)	0 (0.0)	2.19 (1.59-3.0)	0.023
Anemia[6] (n = 6)	6	4 (14.8)	2 (8.0)	2.0 (0.33-12.01)	0.670
Thrombocytopenia[7]	5	5 (18.5)	0 (0.0)	2.13 (1.57-2.89)	0.052
Metabolic alkalosis	4	2 (7.4)	2 (8.0)	0.92 (0.12-7.07)	~ 1
Increased PTT[8]	4	4 (14.8)	0 (0.0)	2.08 (1.55-2.80)	0.112
Intention of poisoning					
Suicidal	38	26 (96.3)	12 (48.0)	28.16 (3.29-240.8)***	<0.001
Accidental	14	1 (3.7%)	13 (52.0)		
Route of exposure					
Oral	48	27 (100.0)	21 (84.0)	2.28 (1.66-3.15)***	0.047
Inhalational	4	0 (0.0)	4 (16.0)		

* Calculated with Fisher's exact test

** Odds ratio for male gender

*** Odds ratio for suicidal intention

**** Odds ratio for oral exposure

[1] Men > 1.2 mg/dL, women > 1.1 mg/dL

[2] Aspartate aminotransferase > 40 U/L or alanine aminotransferase > 56 U/L or alkaline phosphatase > 147 IU/L

[3] Total bilirubin > 2 mg/dL or direct bilirubin > 20%

[4] White blood cell > 11000/mm^3

[5] International normalized ratio > 1.2

[6] Hemoglobin: men < 13.5g/dL, women < 12.0 g/dL

[7] Platelet < 150000/mm^3

[8] Partial thromboplastin time > 35 sec

in higher mortality (13,22). In the present study suicidal intention was one of the predictive factors of death in PQ poisoning with a high OR. The importance of suicidal intention as a risk factor for mortality has been established in number of studies (9,13,16,23). Moreover, suicide by PQ was significantly more common among men similar to a study in Korea (13), which shows the strength of men's intent for suicide and hence choosing a highly potent substance.

LIMITATIONS

In this study similar to the study by Lee et al (17), we found that volume of PQ consumed by the patients was associated with fatality. However, the value of this finding was limited as the volume of poison consumed could only be obtained from the history given by the patients or their relatives which is not a reliable method for measurement of the amount of poison. Moreover, the amount of poison consumed could be asked from patients (or their relatives) who were poisoned from oral route not inhalational. In many studies these limitations have been prevented by analysis of plasma (or urine) PQ concentrations (17,24,25). It has been established that PQ poisoning prognosis is greatly associated with time-related plasma PQ level (24,25). However, the measurement of plasma PQ concentration is not available in every hospital including ours, which can be another limitation of this study. Nevertheless, our findings can help medical toxicologists and emergency physicians to anticipate patients prognosis at emergency settings where simple routine laboratory examinations such as ABG, renal and liver function tests are more commonly and easily available.

CONCLUSION

PQ poisoning is associated with high mortality requiring an immediate assessment of patients and prediction of prognosis. Renal and hepatic failure in addition to respiratory distress can be the strongest risk factors for poor prognosis in acute PQ poisoning.

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