Predictors of Mortality in Paraquat Poisoning: A Two-Year Retrospective Analysis From A Tertiary Care Teaching Hospital in South India

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Abstract

Backgrounds: Paraquat is a major cause of fatal poisoning in agro-based countries like India. Being, a veiled offender it is often deluded for its relatively less fatal counterpart i.eorganophhosporous compounds. It is a highly lethal herbicide, contributing to a majority of the pesticide poisoning related deaths & Disability Adjusted Life Years (DALY) globally.

Methods: A retrospective record review of the patients presenting with paraquat poisoning to the Emergency Medicine Department of a tertiary care center in South India,between August 2014 to August 2016 was done. Demographics, clinical presentation, and laboratory data of patients were analysed to study risk factors associated with morbidity & mortality.

Results: 91 case were evaluated, of which 65.9% were male and majority (78.1%) belonged to the age group 20-30 years and 31 (34%) being agriculturists. 85 (93.4%) attempts were suicidal in nature. Most common presenting symptom was vomiting 72 (79.1%), 27% of the patients had hypoxia (pao2<70%) however the initial mean circulatory assessment were within stable limits (HR- 84/min, BP- 124/78mmhg). Investigations revealed average serum creatinine of 2.8mg/dL (+ 3.16) and bicarbonate of 17.6 mg/dL (+ 4.47). Treatment measures included gastric lavage (67%) and haemoperfusion (49.5%) amongst others.47 (51.6%) patients died with the most common cause of death being Multiorgan dysfunction syndrome -MODS (61.7%) and Acute Kidney Injury-AKI (29.7%).To determine predictors of mortality, univariate and multivariate analysis [adjusted odds ratio (95% confidence intervals)] was done which revealed low bicarbonate6.174[1.20-31.59] and hypokalemia4.79 [1.08-21.19] to be significant risk factors.

Conclusion: Paraquat poisoning has a high disease burden and concerning mortality ratesespecially in young and middle aged adults.Risk factors for mortality include low bicarbonate, hypokalemia and increased serum creatinine with AKI and MODS being the most common causes of death.

Keywords :*Paraquat, agricultural chemicals, toxicology*

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Introduction

Paraquat (1, 1-dimethyl-4, 4-bipyridium dichloride) ingestion is a major cause of fatal poisoning in South East Asia(1).In the Indian subcontinent, it is freely available in the market in the form of liquid concentrate with concentration ranging from 20% to 42%. Paraquat

is a weedicide that has a rapid action, destroying plant tissue on contact, by translocation within the plant however, this product is also highly toxic to humans and most animals.[2,3]. Absorption of paraquat against a concentration gradient into the lungs stimulates inflammatory response with leukocyte recruitment which subsequently sequels to late pulmonary fibrosis that inevitably leads to hypoxemia paradoxically potentiated by oxygen therapy[4,5]. It is also known to cause acute kidney injury and multi-organ failure[5]. As the associated mortality rates are very high, prognostic indicators of the outcome are important to help guide therapy in the ED. Parameters such as plasma and urinary paraquat concentrations and serum creatinine have been identified as prognostic markers in Asian studies.[6] Such data does not exist in the Indian context.

By this retrospective record review, we aimed to describe the profile of cases of paraquat poisoning and hypothesize the demographics, clinical presentation, and laboratory data as risk factors and evaluate which of them could serve as mortality predictors.

Methods

The cross-sectional study was conducted at the Emergency Medicine Department of a tertiary care teaching hospital in South India. All consecutive adult patients with a history of paraquat intake and/or identifying the container with paraquatbetween August 2014 to August 2016 were included in the study. A retrospective record review of the patients was done. The institutional ethics committee (IEC 702/2018) approval was obtained and strict patient confidentiality was maintained. The records were scrutinized for demographics, the clinical presentation including presenting symptoms and vitals on arrival. Laboratory data such as arterial blood gas, complete blood count, renal and liver function tests were also included. The data was analyzed and demographic details, clinical presentations (signs and symptoms), and investigations were hypothesized as risk factors of mortality and were subjected to univariate and multivariate analysis to look for meaningful association.Records with incomplete data were not included in the analysis.

We entered data on Epi Info 7 and performed statistical analysis using SPSS ver 16.0 (SPSS Inc., Chicago, IL, USA). The demographic characteristics were summarized using descriptive statistics. All the hypothesized predictors of mortality were initially subjected to a univariate binary logistic regression after excluding discharge against medical advice (DAMA) patients. It was decided prior that any factor with $p < 0.2$ in univariate analysis would be subjected to multivariate analysis. The modes of treatment did not fulfill this criterion and hence a multivariate analysis model was not constructed for the same. However, few laboratory parameters fulfilled the criteria and multivariate analysis was done using binary logistic regression. To avoid multicollinearity, blood urea, and Alanine aminotransferase (ALT) were not included in the model.

Results

The total number of paraquat poisoning cases presenting to our Emergency Department(ED) was 91 of which 65.9% were male. The demographic data, clinical findings, and laboratory investigations were grouped into two namely survivors and non-survivors based on outcome at 72hrs from hospital presentation. (Table1) The mean (+SD) age of patients was 29 (+11.93) yearswith the majority 78.1% being young adults, between 20-30 years. We found nearly one-third, 34%, of our patients were agriculturists and an overwhelming majority (93.4%) were cases ofdeliberate self-harm. The most common symptom was vomiting (79.1%)followed by oral erosions (51%).The majority of patients at presentation were not in shock, with the mean heart rate(HR) of 84/min and blood pressure(BP) of 124/78mmhg. Our hospital was the first point of contact with health services for 34 (37.4%) of patients while the remaining cases were referred from lower health centers for tertiary care,. .The investigations done in ED revealed a mean total count was 15,582.56 and the mean blood urea and creatinine of 47.15 and 2.82 respectively. 27 (29.7%) patients had Blood urea > 40mg/dL, 36 (39.6%) had Serum creatinine > 2mg/dLand 18 (19.8%) had AST> 100U/L. Arterial Blood Gas (ABG) analysis revealed a mean pH of 7.32 and bicarbonate of 17.66 indicating an underlying metabolic acidosis. The methods of treatment included the use

of gastric lavage 61 (67%) and renal replacement therapy like haemoperfusion 45 (49.5%) and haemodialysis 33 (36.3%).Of the 91 patients in the study, 47 (51.6%) died of which 20 (22.0%) died within 24 hours (Table 2).23 (25.3%) patients survived till hospital discharge & 21 (23.1%) were discharged against medical advice & were telephonically followed up for outcome.

Table 1: Demographic and clinical profile of patients

Variable	Category	Non-survivors n=47	Survivors n=44	Total sample n (%)	P value
Age (n=91)	10-20 years	10	13	23 (25.27%)	0.129
	21-40 years	27	28	55(60.43%)	
	> 40 years	10	03	13(14.28%)	
Gender (n=91)	Male	29	31	60(65.93%)	0.378
	Female	18	13	31(34.06%)	
Occupation (n=91)	Agriculture	22	09	31(34.06%)	0.51
	Student	07	12	19(20.87%)	
	Others	15	26	41(45.05%)	
Manner of consumption (n=91)	Suicidal	45	40	85(93.4%)	0.153
	Homicide	02	0	02(2.19%)	
	Accidental	0	04	04(4.39%)	
Toxin use variables#	Vomiting	39	33	72(79.12%)	0.6902
	Oral Erosions	19	27	46(50.54%)	
	Abdominal Pain	10	11	21(23.07%)	
	Breathlessness	09	07	16(17.58%)	
	Other	09	08	17(18.68%)	
Vitals at presentation	Tachycardia (>100/min)	13	12	25(27.27%)	0.944
	Hypotension (<90/60mmHg)	02	01	03(3.29%)	
	Hypoxia (Spo2 <90%)	05	04	09(9.89%)	
Preliminary Treatment	Straight to our center	20	14	34(37.36%)	0.290
	Referred cases	27	30	57(62.63%)	

Cont... **Table 1: Demographic and clinical profile of patients**

Method of Treatment#	Gastric Lavage	34	27	61(67.03%)	0.265
	Charcoal	07	05	12(13.18%)	0.618
	Haemodialysis	17	16	33(36.26%)	0.98
	Haemoperfusion	27	18	45(49.45%)	0.114
Respiratory Rate (n=91)	0-15	01	03	04(4.39%)	0.547
	16-30	44	39	83(91.20%)	
	31 and above	02	02	04(4.39%)	
Haemoglobin (n=91)	Less than 10	01	03	04(4.39%)	0.275
	More than 10	46	41	87(95.60%)	
Other laboratory parameters	Blood urea (>40mg/dL)	15	12	27(29.67%)	0.628
	Creatinine (>2mg/dL)	22	14	36(39.56%)	0.143
	Elevated Transaminase	12	06	18(19.78%)	0.154

*indicates significance using chi square test. Significance assumed at $p<0.05$

#indicates the variables for which frequency and percent frequency was reported

Table 2: Paraquat related mortality profile

Variable	Category	Frequency (%) [n=47]
Mortality interval (consumption to death)	< 24hours	20 (42.5%)
	24-48 hours	16 (34.0%)
	>48 hours	11 (23.4%)
Cause of Death	MODS	29 (61.7%)
	AKI	14 (29.7%)
	Others (ARDS , Sepsis)	4 (8.5%)

Predictors of Mortality with Paraquatpoisoning: We hypothesized risk factors using the data generated from the records of the patients. This included clinical parameters such as tachycardia,hypotensiontachypnea,hypoxia and laboratory parameters like hemoglobin,total count, blood urea and creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and ABG parameters like partial pressure of oxygen (pO2), carbon dioxide (pCO2) and acidosis (pH).. Besides the above mentioned factors, demographic parameters such as age, gender, and method of treatments were also considered and were subjected to univariate analysis. Risk factors with p value less than 0.2 were then subjected to multivariate analysis. It should be noted that in order to avoid multicollinearity, blood urea and ALT were not included in the model for further analysis. The results of the univariate analysis are listed in Table 3. After multivariate analysis[adjusted odds ratio (95% confidence intervals)],of the five parameters considered, low bicarbonate 6.174(1.20-31.59) and hypokalemia 4.79 (1.08-21.19)were found to be statistically significant risk factors (Table 4).

Table 3: Predictors of mortality (Univariate analysis)

Variables	Exp B /OR[95% CI]	P Value
Sex	3.128[0.95-10.20]	0.059
Age	0.0[0.0-0.0]	1
Occupation	0.172[0.24-3.84]	0.968
Amount	8.66[0.88-84.83]	0.064
Clinical Profile		
Tachycardia	2.12[0.64-7.00]	0.217
Hypotension	0.667 [0.058-7.71]	0.746
Hypoxia	0.728[0.44-6.65]	0.426
Laboratory findings		
Elevated Total Count	8.23[2.78-24.32]	0.000
Elevated Blood urea	3.63 [0.98-13.49]	0.05
Elevated creatinine	6.28 [1.70-23.14]	0.006
Low Potassium	1.96[0.51-7.51]	0.326
Elevated ALT	0 [0.00-0.00]	0.998
Elevated AST	5.03[1.55-16.37]	0.007
Low PO2	1.22[0.3-4.97]	0.779
Low HCO3	0.160[0.044-0.57]	0.005

Cont... **Table 3: Predictors of mortality (Univariate analysis)**

Treatment		
No preliminary treatment in referring hospital	0.664 [0.24-1.82]	0.429
Gastric lavage not done	1.43 [0.53-3.84]	0.46
Haemodialysis not done	1.41 [0.513-3.9]	0.502
Haemperfusion not done	0.684 [0.26-1.77]	0.434

Ex (B) – exponentiation of the B coefficient or odds ratio

Table 4: Predictors of mortality (Multivariate analysis)

S. No	Variables	Exp B/OR [95% C.I]	P value
1.	Gender	1.503[0.41-5.48]	0.537
2.	Amount of dose	0.0[0.0-0.0]	0.249
3.	Low Potassium	4.79 [1.08-21.19]	0.039*
4.	Elevated creatinine	0.781[0.11-5.40]	0.802
5.	Low HCO3	6.174[1.20-31.59]	0.029*
6.	Elevated AST	1.306 [0.19-8.90]	0.785
7.	Elevated total count	1.003 [0.96-1.037]	0.878

*significant as $p<0.05$

Ex (B) – exponentiation of the B coefficient or odds ratio

Discussion

Paraquat is a nonselective, fast-acting herbicide that is environmentally harmless due to its rapid decomposition into nontoxic compounds after soil contact however poses a significant risk to humans on consumption [(7)]. The mortality associated with it is as high as 50-90%[(8)]

In our study, the mean age of the patients was 28.74 which was consistent with the study done by Tanuj et al[(8)]. Being a weedicide, it was unsurprising to find that agriculturists formed nearly one-third of the affected patient population, however, a remarkable number of patients were students and those between 20-30 years of age.

On presentation to the department, the mean vitals (pulse, BP, respiratory rate) of our patients was stable,comparable to the study by Hong et al in South Korea [(6)]. We also found that tachycardia (27.5%), hypotension (3.3%), and even hypoxia (27.7%) are uncommon signs of the initial presentation of our patient profile as compared to patients with Organophosphate poisoning who generally present with severe symptoms[(9)]. Local toxic effects of paraquat such as oral erosions and ulcers were previously documented[(9)] and in our study, we noted a similar occurrence in about 46 (50.5%) of the cases, however, the most common symptom was vomiting 72 (79.1%). In terms of initial

laboratory parameters, mean total count was elevated as compared to the study done by Hong et al[6], however, the mean creatinine was higher and the mean pH was found to be lower in our study. Our analysis also found that 40% of patients had a serum creatinine value higher than 2mg/dLand 30% blood urea more than 40mg/dL , further establishing the toxic renal effects of paraquat ingestion.[10]Unfortunately, no standard guidelines exist for treatment paraquat toxicity and hence a variety of modalities are tried. Depending on their time of presentation to the department initial modalities such as gastric lavage 61 (67%) and charcoal 12 (13.2%) were tried which have been well documented in previous studies.[1,6,10]

We found the mortality to be 51.6% which was consistent with both Asian and Indian studies [8,10] done previously. As demonstrated by Rao R et al[1] the use of early haemoperfusion has shown mortality benefits, 45 (49.5%) and 33 (36.3%) of our patients underwent haemoperfusion and hemodialysis respectively. On the contraryPond &Tominack et al reported thathaemoperfusionwas not found to be useful in potentially lethal concentration of paraquatdue to accumulation in highly vascular tissues of the vital organs and pneumocytes before the initiation of haemoperfusion, further retreating the extreme toxicity of the agent [10]. The most common cause of death in our study was Multi Organ Dysfuction Syndrome MODS (61.7%) and isolated Acute Kidney Injury-AKI (29.7%) consistent with the study done by Jagadeesan M et al[11] albeit in a much smaller cohort. MODS can be explained by the inhibition of reduction of NADP to NADPH which results in the accumulation of superoxide and free radicals which causes destruction of lipid cell membranes. Paraquat is mainly eliminated by kidney and acute kidney injury is the end result of that.

Various studies have identified a number of factors that predict mortality in paraquat toxicity. A host of parameters like demographics, clinical parameters, and laboratory investigations were considered for the same. In a study by Hsu et al, age over 60 years, suicide attempts, and hypothermia were found to be significant risk factors for paraquat-related fatality. Interestingly, in our study female gender was found to be significant as per the univariate analysis, which was contrasting from the findings of Sun et al[12]. The fatality of paraquat poisoning is depended on renal, hepatic function, and acid-base status which has been demonstrated before. [6,13] These results could be attributed to the multiorgan involvement by the toxin. Our findings were consistent with it as the results of univariate analysis revealed lab parameters like elevated creatinine, hypokalemia, acidosis, and raised AST as mortality markers. Further multivariate analysis revealed low bicarbonate and hypokalemia to be significant mortality indicators. Low bicarbonate is a familiar factor as it has been mentioned in studies done in South Korea[6,12], although unlike our findings they did not find it to be statistically significant. Hypokalemia has not been found as a mortality marker as per our review of literature and as mentioned before even though we found it to be statistically significant, it cannot be independently considered as a risk factor. On the other hand, creatinine has been earlier found to be a mortality indicator, Elenga et al[3]found 50% of adult patients with creatinine 120 µmol/L (1.35 mg/dL) on admission, died and another study in 2009 on 278 patients showed that an elevated creatinine level over 120 µmol/L (1.35 mg/dL) on admission was a significant predictor of mortality[13] Our findings of serum creatinine wereconsistent with the literature however, the small sample size could be a reason for it to be not statistically significant.

Our study had a few limitations, we do not have the facility for quantitative plasma paraquat measurement for our patients which has been widely found as a direct mortality marker.During data collection, exact mortality times were not available for few records and hence that data was collected as a grouped variable. Hence we could not do a survival analysis, which would have been a better statistical tool. Also, we have considered only a cross-sectional look at clinical findings and laboratory data and have not included serial monitoring of the parameters.

Conclusion

Paraquat is silently emerging as a compound to watch out for with its increasing numbers and high mortality rates owing partially to the lack of an antidote. Unchecked sale of pesticides and weedicides, which are

available as over the counter items has unfortunately resulted in a high patient load presenting with deliberate self-harm with such agents. With high fatality in young productive population of predominantly low and middle-income agro-based countries, it calls for more research and legislative controls to mitigate the same.

The initial clinical presentation of these patients might be unremarkable unlike its usual comparator i.e. organophospate compounds, however, the laboratory investigations form a valuable set of tools for prognostication. The lack of plasma paraquat concentration assessment should not be a deterrent, instead of routine laboratory parameters like renal function tests, liver function tests and ABG are reliable predictors of mortality and can guide treatment and ignite future research on clinical management.

List of abbreviations

Emergency Department	ED
Discharge against medical advice	DAMA
Alanine aminotransferase	ALT
Aspartate aminotransferase	AST
Multi organ dysfunction syndrome	MODS
Acute Respiratory distress syndrome	ARDS
Acute Kidney Injury	AKI
Arterial Blood Gas	ABG
Partial pressure of oxygen	pO2
Partial pressure of carbon dioxide	pCO2
Bicarbonate	HCO3

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