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ORIGINAL RESEARCH

The Clinical Spectrum and Predictors of Early Mortality in Patients with Paraquat Intoxication: A Study from North India

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Abstract

Introduction: Paraquat is (N, N´-dimethyl-4, 4´-bipyridinium dichloride; PQ), is an effective herbicide which has increasingly been used for self-harm. PQ exerts injurious effects through oxidative stress and mitochondrial dysfunction but therapy with antioxidants and immunosuppressants has not been helpful. As currently there is no plausible antidote for acute paraquat toxicity, there is a need to study the predictors of mortality and outcome.

Aim: To study clinical spectrum and predictors of early mortality in patients of intoxication.

Method: The study was conducted from July 2019 to Dec 2021. Patients fulfilling the diagnostic criteria i.e., acute paraquat intoxication were included and relevant investigations were done. Patients with history of chronic lung, kidney, heart, or liver disease were excluded.

Result: In our study, 15 out of 18 patients were male and mean age of presentation being 25 yrs. Breathlessness being the most common symptoms of presentation, while 50% of patients had paraquat tongue. Out of 18 patients just a single patient had survived with mortality of 94.4%. Patients with early mortality had ingested double the dose of paraquat and manifested most severe renal and hepatic dysfunction as compared to the late mortality group.

Conclusion: The mortality in patients with paraquat ingestion is positively correlated with dose of ingestion. Our results showed that the eGFR (Estimated glomerular filtration rate) and SOFA (Sequential organ failure assessment) score can serve as the predictors of early mortality in paraquat intoxication. SOFA scores are simple and easy to perform and include parameters of lung, liver and kidney which are the major organ systems affected in paraquat intoxications.

Keywords: Paraquat, Toxicity, Poisoning, Mortality

Introduction

According to a report released by World Health Organization in 2014, acute pesticide intoxication is a common method of suicide globally (1). Pesticide intoxication remain the third most common method of committing suicide in 2010. Pesticides include bactericides, baits, fungicides, herbicides, insecticides, lures, rodenticides, and repellents. Paraquat (PQ) is a widely used bipyridyl contact herbicide with a good safety record when used properly but can cause substantial morbidity and mortality following ingestion. By blocking photosynthesis-related reduction of oxidized coenzyme II (NADP þ) into reduced coenzyme

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II (NADPH) in plant cells, paraquat leads to accumulation of reactive oxygen species and cell death, thus achieving rapid weeding (2).

There are three degrees of severity for PQ poisoning (3). Mild poisoning causes oral irritation and gastrointestinal upset but eventually results in complete recovery. Moderate to severe poisoning produces acute renal failure and in severe cases acute hepatitis followed by pneumonitis or pulmonary fibrosis, often leading to death in 2–3 weeks. Acute fulminant poisoning results in death within a week due to multisystem organ failure and cardiovascular collapse. The mechanisms of PQ toxicity involve generation of the superoxide anion, which leads to both the formation of more toxic reactive oxygen species, such as hydrogen peroxide and hydroxyl radicals. Further, the oxidation of the cellular NADPH (Nicotinamide adenine dinucleotide phosphate), the major source of reducing equivalents for the intracellular reduction in PQ, results in the disruption of important NADPH-requiring biochemical processes. The primary cause of mortality in PQ poisoning is respiratory failure due to an oxidative insult to the alveolar epithelium with later obliterating fibrosis or acute respiratory distress syndrome.

Paraquat (N, N´-dimethyl-4, 4´-bipyridinium dichloride; PQ) is one of the most widely used herbicides in the world. PQ is a widely used suicide agent in developing coun-tries due to its widespread availability. PQ intoxication is a serious public health prob-lem, with an estimated annual incidence of 2000 toxic ingestions associated with a mortality rate of 60-70% in some Asian coun-tries (3-7). It has a highly toxic effect on humans, and its minimum lethal dose is 30 mg/kg. There is no specific antidote for acute paraquat intoxication. Limited literature is available from the Indian subcontinent regarding the predictors of severity and early mortality in paraquat intoxication. Thus, this study aims to study early and effective predictors of adverse outcome in paraquat intoxication and can be useful for more focused management of patients with paraquat intoxication. The study was planned to study the clinical features and predictors of early mortality in all the patients of paraquat intoxication.

Materials and methods

It was a hospital based descriptive study conducted on patients with paraquat intoxication presenting in Department of Medicine, Guru Gobind Singh Medical College and Hospital, Faridkot. Both retrospective (i.e., July 2019 – June 2021) and prospective (i.e., July 2021-December 2021) data of all patients of acute paraquat intoxication was collected and analysed. Patients with a history of serious chronic diseases, such as heart, liver, kidney, and lung diseases and patients of paraquat intoxication combined with other drug poisoning were excluded from the study.

Results

A total of 18 cases of acute paraquat intoxication were included in our study. Most patients were male i.e., 15 (83.3%). The average age of presentation was 25 yrs. (ranging from 15 to 45yrs). Fourteen patients were admitted more than 24hrs after paraquat ingestion. The average delay in presentation was 2.94 days. Among the 18 patients, there was just a sole survivor. The most common presenting symptoms were breathlessness followed by jaundice and decreased urine output. Oral ulcers and paraquat tongue were also seen in 50% of patients. Various presenting features are mentioned in the table below:

Table 1: Clinical Characteristics of Paraquat Poisoning

Presenting Clinical Features	N
Vomiting	9
Oral ulcers and paraquat tongue	9
Decreased urine output	11
Jaundice	12

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Breathlessness	13
Abdominal pain	1

The dose of paraquat ingested is directly proportional to the mortality as suggested by the earlier reported studies (8,10-12). In our study, the average amount of paraquat consumed was 80mL in patients with early mortality as compared to 35mL in patients with delayed mortality. Before starting any treatment, patients were investigated as depicted in the table 2 below:

Table 2: Baseline Characteristics of patients with acute paraquat poisoning

Number of Patients	18
Age (Yrs.)	25+/-8.4
Sex	15male 3 female
Toxic Dose (ml)	50+/-32
Total leukocyte count (x 10^9/L)	9700+/-6500
Platelet count	229+/-135
Haemoglobin (g/dl)	11.9+/-1.2
Biochemical Investigations	
ALT (5-40IU/L	154+/-25
AST(5-35IU/L)	201+/-42
ALP (60-150IU/L)	243+/-51
TSB (0.3-1.1mg/dl)	5.7+/-0.9
ALB (3.3-5.5g/dl)	3.6+/-0.5
Urea(15-45mg/dl)	118+/-95
Creatinine (0.8-1.3mg/dl)	5+/-4.5

The results showed deranged hepatic (66.65%) and renal function tests (61%) in majority of the patients. Fifteen patients had transaminitis (83.33%) with more than 2 times elevated enzymes while 10 patients had elevated alkaline phosphatase (55.5%). Chest X-ray showed parenchymal infiltrates in 8(44.4%) and consolidation in 5(27.7%) patients, while X-ray was normal in 6(33.3%) patients. The most common abnormality in blood gas analysis was metabolic acidosis and respiratory acidosis, both seen in 6(33.3%) patients each. Respiratory involvement was there in 66.6% of patients as show below.

Organ involved	
Total patients	18(100%)
Oral Ulcers	9(50%)
Acute renal failure	11(61%) 8HD
Hepatic failure	12(66.6%)
Respiratory failure	12 (66.6%) 4 Venti/NIV 8 oxygen

Out of 18 just a single patient survived, the mortality is 94.4% (17/18). Six out of 18 patients died in less than 7 days after the ingestion and the remaining mortalities were on day 7 or beyond. The patients with early mortality were having more renal and hepatic dysfunction as compared to the group with late mortality. Also, the dose of paraquat ingested was more than double the average dose seen in late mortality group. SOFA score was calculated and it was also increased in early mortality group.

	Early mortality	**Late mortality**
Patients	6	11
Creatinine(mg/dl)	6.58	4.28
TSB (mg/dl)	6.6	5.2
PQ dose(ml)	80	35
GFR	25.3	63.6

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SOFA score	7.8	5.8

The results suggest that there is no as such single marker of early mortality except the dose of paraquat ingested. SOFA score can be used as the marker for early mortality as it includes the variables from respiratory and hepato-renal involvement. Also, eGFR can also be used as the marker for early mortality.

Discussion

Paraquat, is a dipyridyl compound used for weed control in most of the countries. It has been banned in 32 countries and sale is also restricted in few because of health concerns and lack of availability of antidote and high mortality (9). In consensus with the previously reported studies, our study also showed that the mortality in paraquat poisoning is positively correlated with dose, plasma, and urinary concentrations (10,11,12). The determination of plasma and urinary concentration is highly technical and expensive and only few centres are equipped with these instruments. The determination of paraquat in body is difficult, especially because there are only few variables like vomiting or gastric lavage. Therefore, other methods to predict the prognosis are also needed.

Our results showed that the eGFR and SOFA score can serve as the predictors of early mortality in paraquat intoxication. Ingestion of large amounts is considered to be fatal from multiorgan failure and cardiogenic shock. According to the toxicokinetic process of paraquat, the kidney is also a main target organ after poisoning (13). A total of 90% of paraquat is excreted from the kidney in its original form within 12 to 24 hours (14). The mechanisms of paraquat induced acute kidney injury (AKI) include oxidative stress, inflammatory response, apoptosis, and renal hemodynamic changes (15-17). Some clinical studies have also showed that paraquat-induced AKI precedes acute lung injury, peaks within the next 3 to 5 days, and then returns to normal renal function in some patients within 3 weeks (18-19). The degree of renal damage caused by acute paraquat intoxication greatly varies. The main pathological manifestations of acute paraquat intoxication are acute tubular necrosis and ischemic glomerulopathy. Mild cases may manifest as simple urinary abnormalities, such as proteinuria and/or haematuria. However, severe cases may manifest as acute renal failure and even require renal replacement therapy (19). The prognosis of AKI with acute paraquat intoxication is poor.

In our study, the incidence and mortality rates of AKI were 77% which is in consensus with the earlier studies which also showed the incidence of 46.6-85.4% (2,20). Our study revealed that GFR in the patients who died in the first week of poisoning was half as compared to the patients who died later. Thus, the outcome was related to the severity of AKI. Therefore, GFR should be investigated as a marker of early mortality in paraquat intoxication. Our finding was consistent with hepatic injury following paraquat ingestion, evident by transaminitis and cholestasis. Florabel G et al hypothesized that paraquat injury to liver is biphasic, initially it is hepatocellular followed by chloangiocellular after 48hrs. While the fatality rate ranges between 35-62% around the world, in indigenous studies it was found to be around 60-70% (21,22). Our study showed in-hospital mortality rate of 94.4%. This could be attributable to the delayed presentation of around 2.94days after paraquat ingestion as the golden hour of treatment was lost in all patients.

Various scoring systems have previously been proposed as mortality predictors for patients with paraquat intoxication (11,19–21). Models based on SOFA scores performed second to APACHE II/III scores only. Cholangitis et al. proved that SOFA scores had the best discriminative ability (AUC = 0.79) when compared to APACHE II scores, Model for End-Stage Liver Disease (MELD) scores and King' s College Hospital (KCH) scores (21). As per the study done by Craig et al, SOFA scores 7 during the first 96 h post-overdose predicted death/transplantation with a sensitivity of 95.0 (95% CI, 78.5– 99.1) and a specificity of 70.5

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(95% CI, 66.3–71.6) (23). SOFA scores include parameters of lung, liver, and kidney which are the major organ systems affected in paraquat intoxication. Also, the SOFA score is a simple, easy to perform, and reproducible. Thus, it is better to use SOFA score in these patients and SOFA scores can therefore aid in predicting the prognosis for paraquat intoxication.

In summary, our data proves that SOFA and eGFR, which are based on the extent of multiple organ failure, can help in predicting early mortality in paraquat poisoning. The limitations of our study were small sample size, retrospective nature of study and short follow-up time. However further studies are needed to find patients with delayed on set lung injury and fibrosis.

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