



Acute Kidney Injury in Paraquat Poisoning : A Study of 400 Cases

Abstract

Background: Paraquat (PQ) a synthetic weedicide is often consumed with the intent to commit suicide. PQ can accumulate in the lungs and kidneys through redox reactions, generating reactive oxygen species (ROS) and causing severe pulmonary fibrosis and acute tubular necrosis. Literature on PQ-acute kidney injury (PQ-AKI) is limited. **Materials and Methods:** We reviewed data on patients referred to nephrology services to manage PQ-AKI between June 2014 and June 2024. We analyzed epidemiological data, clinical features, and outcomes. **Results:** Four hundred patients were analyzed. The mean age was 30 ± 11 years. Of 1342 PQ admissions, approximately 30% developed AKI, with PQ-AKI accounting for 6.2% of all cases with AKI during the period. Oligoanuria and deranged kidney function were reasons for referral. The majority were in stage 3 AKI (75%), of whom 45% received hemodialysis (HD). The mortality rate (75%) was associated with consumption quantity, gender, and multiorgan failure. **Conclusion:** PQ-AKI is an important contributor to AKI in this region and is associated with high mortality. Quantity of consumption, gender, multiorgan failure, and latency in seeking medical care were associated with outcomes.

Keywords: AKI, India, Mortality, Paraquat, Tropical AKI

Introduction

Paraquat (PQ), N, N'-dimethyl-4, 4'-bipyridinium dichloride, is a synthetic, quaternary, nitrogenous, organic compound.¹ It is a non-selective contact pesticide that also destroys weeds by forming superoxide anions during photosynthesis. PQ poisoning is becoming a serious public health concern, especially in developing countries, due to easy access and lack of awareness of potential harm. Exposure can occur accidentally or intentionally. PQ accumulates in the lungs and forms free radicals causing lipid peroxidation. NADPH gets depleted, causing diffuse alveolitis and extensive pulmonary fibrosis, leading to respiratory failure. Severe poisoning affects the liver, kidneys, and lungs, and respiratory failure primarily causes death.²

Decreased absorption by gastric lavage and oral activated charcoal; elimination by conventional hemodialysis (HD), hemoperfusion (HP), continuous veno-venous hemofiltration, and continuous renal replacement therapy (CRRT); decreasing inflammatory response using immunosuppressants (corticosteroids and cyclophosphamide); antioxidants (N-acetyl

cysteine, Vitamin C); and a combination of therapies were used to treat patients with PQ intoxication with varying outcomes.³⁻⁵

PQ is one of the important causes of tropical acute kidney injury (AKI). This compound is readily available and commonly used in India. PQ-AKI is associated with high morbidity and mortality rates. However, the literature is limited to case reports and case series.⁶ We undertook this study to analyze the clinical features and outcomes of PQ poisoning.

Materials and Methods

This is a ten-year retrospective review of records of patients admitted to nephrology services for PQ-AKI management between 2014 and 2024 at Gandhi Hospital, Hyderabad, Telangana. AKI was defined according to definitions given by KDIGO, 2012.⁷

PQ poisoning was diagnosed based on an alleged history of consumption and clinical presentations. We did not estimate PQ blood levels or test for urine dithionite positivity. PQ poisoning was classified based on consumed amounts as "mild" if the consumption was < 20 mL, "moderate" if 20-40 mL, and "high" if > 40 mL.

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Patients were treated with gastric lavage, followed by oral steroids, N acetylcysteine, and vitamin C. Dialysis was given as indicated for patients with AKI. We obtained the Institute Ethics Committee's approval and patient consent was obtained. We assessed demographic details, latency of referral, lab parameters, mode of renal replacement therapy, kidney injury outcomes, and factors affecting mortality.

Patients' baseline characteristics, presumed causes, clinical presentation, outcomes, and management were analyzed using descriptive statistics. The data were presented as patients' number (%), mean and standard deviations (SD). Factors potentially associated with death were analyzed using the t-test for continuous variables, Chi-square test, or Fisher's exact test. We examined the variables using multivariate logistic regression to predict mortality. The analyses were conducted using SPSS software version 28.0, and p-values < 0.05 were considered statistically significant.

Results

The study included 400 patients with PQ-AKI. The study age range was 6 to 70 years, averaging 30.7 ± 11.1 years. Suicide and inadvertent consumption account for 90% and 10% of PQ poisoning cases, respectively. Amongst accidental ingestion cases, alcohol intoxication mostly led to PQ consumption. Quantity of consumption was mild in 53%, moderate in 30%, and high in 16% of patients [Table 1]. Most typically, PQ was consumed with soft drinks/alcohol. PQ is a readily available and unrestricted weedicide. The mean latency in seeking medical care and nephrology referral was 1.28 ± 1.24 and 3.4 ± 2.5 days, respectively.

Vomiting (87%) was the most typical gastrointestinal symptom, followed by abdominal discomfort (31%), oral ulcers (63%), jaundice (29%), oliguria (40%), and breathlessness (26%). Referral to nephrology was primarily due to oligoanuria (45%). KDIGO staging confirmed stage 1 AKI in 13%, stage 2 in 8%, and stage 3 in 78% of patients [Table 1].

Oliguria and raised renal parameters most frequent indications for kidney replacement therapy (KRT) (72%). HD (42%), followed by peritoneal dialysis (16%) were most used. However, since CRRT and HP were available for the last two years, both treatments were done in 19% of patients each.

The mean serum creatinine in our cohort was 5 ± 3 mg/dL [Table 2]. Raised liver function parameters with mild transaminitis and hyperbilirubinemia were noted in a few patients.

The study's primary outcome, mortality, was high (75%). Significant contributors to this were Acute respiratory

Table 1: Demographic characteristics

Baseline characteristics	
Age (years)	30.77 ± 11.16
Sex	
Males	300 (75%)
Females	100 (25%)
Amount of PQ	
Mild	212 (53%)
Moderate	122 (30.5%)
High	66 (16.5%)
Reason for consumption	
Suicidal	361 (90.3%)
Latency	
Latency to first medical care (days)	1.28 ± 1.24
Latency of nephrology referral (days)	3.24 ± 2.5
Clinical presentation	
Vomiting	350 (87.5%)
Oral ulcers	253 (63.25%)
Oliguria	162 (40.5%)
Pain abdomen	125 (31.2%)
Jaundice	117 (29.2%)
Breathlessness	104 (26%)
Dysphagia	65 (16.2%)
Malena	24 (6%)
Indication of KRT	
Metabolic acidosis	81 (20.7%)
Raised renal parameters	126 (31.5%)
Renal symptoms	
Anuria	21 (5.38%)
Oliguria	162 (41.5%)
Nonoliguria	207 (53.07%)
AKI stage 1	53 (12.5%)
AKI stage 2	33 (8.2%)
AKI stage 3	314 (78.5%)
Mode of KRT	
Hemodialysis	169 (42.2%)
CRRT	79 (19.7%)
Peritoneal dialysis	66 (16.5%)
Hemoperfusion	76 (19%)
No KRT	10 (2.5%)
Complication during RRT	17 (4.2%)
Days of hospital stay	6.9 ± 3.7
Ventilatory support	116 (29%)
Primary outcome	
Death	295 (73.7%)
Survival	105 (26.2%)
Secondary outcome	
Renal recovery (complete)	93 (23.2%)
Renal recovery (partial)	12 (3%)
Cause of death	
ARDS	190 (47.5%)
Aspiration pneumonia	1 (0.3%)
MODS	102 (34.5%)
Sudden cardiac death	2 (0.5%)

KRT: Kidney replacement therapy, AKI: Acute kidney injury, CRRT: Continuous renal replacement therapy, ARDS: Acute respiratory distress syndrome, MODS: Multi organ dysfunction syndrome

Table 2: Lab parameters

Hemoglobin (gm/dL)	11.6 ± 1.8
Total leucocyte counts (per mm ³)	11998.8 ± 5013.7
Serum creatinine (mg/dL)	5.04 ± 3.4
pO ₂	84.79 ± 15.41
Total bilirubin (mg/dL)	3.94 ± 4.25
Direct bilirubin (mg/dL)	2.26 ± 2.49
SGOT (U/L)	92.08 ± 83.21
SGPT (U/L)	101.5 ± 87.94

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

distress syndrome and multi-organ involvement [Table 3]. Regarding secondary outcomes, 23% and 3% of patients had complete and partial renal recovery, respectively. We could not include the present study's short-term/long-term follow-up details.

Univariate analysis for determinants of mortality revealed a statistically significant association between variables such as quantity of consumption, gender, severe acidosis, and multiorgan failure ($p < 0.05$). The variables mentioned above were statistically significant in multivariate analysis [Table 4].

HP was given to 19% of patients, and all admitted within 72 hours of consumption, followed by CRRT in case of multi-organ failure or conservative management in those without multi organ system failure (MOSF)/AKI and HD/PD in those with AKI. HP was given for four hours on the day of admission. The HP group showed better survival outcomes [Table 5].

Discussion

The PQ-AKI incidence is 29% and 6.2% in all PQ and AKI admissions, respectively. Our study encompasses 400 PQ-AKI patients over 10 years. It is the largest in existing literature. The primary outcome, mortality, was high, like related to the severity of poisoning and delayed referrals. KRT strategy was selected based on hemodynamic stability. Most patients were in multi-organ failure, needing supportive systems at admission.

In our study, we gave HP within 72 hours of PQ consumption. Our findings are contrary to reports of HP within four hours of consumption. The lower AKI stages and CRRT following HP in survivors may have increased survival rates in the HP group. Hence, survival cannot be solely attributed to HP and needs future assessment for confirmation.

Literature regarding PQ-induced AKI predominantly comprises case reports and series.^{8,9} A diverse range of AKI incidence (50-100%) was documented among patients admitted with PQ toxicity. In the present study, we observed the incidence of AKI to be 29%. Our study represents the most extensive study conducted to date.

Table 3: Factors affecting mortality

Parameter	Survivors	Non-survivors	p-value
Age (years)	31.5 ± 12	30.6 ± 10.9	0.483
Sex			
Males	71 (67.6%)	229 (77.6%)	0.042*
Females	34 (32.4%)	66 (22.4%)	
Latency to first medical care (days)	1.24 ± 1.11	1.31 ± 1.28	0.644
Latency to referral (days)	3.13 ± 1.91	3.28 ± 2.68	0.597
Amount of PQ			0.032*
Mild	90 (42.46%)	122 (57.54%)	
Moderate	13 (10.7%)	109 (89.3%)	
High	0	66 (100%)	
Serum creatinine (mg/dL)	5.6 ± 3.3	4.9 ± 3.5	0.088
Hemoglobin	11.5 ± 2	11.7 ± 1.8	0.368
WBC (per mm ³)	11119.5 ± 5668.6	12307 ± 4735.1	0.059
pH	7.4 ± 0.1	7.4 ± 0.2	0.021*
pO ₂	89.8 ± 12.9	83.1 ± 15.9	<0.001*
Total bilirubin (mg/dL)	3 ± 3.4	4.3 ± 4.5	0.002*
Direct bilirubin (mg/dL)	1.6 ± 2.1	2.5 ± 2.6	<0.001*
SGOT (U/L)	66.5 ± 58.5	101.3 ± 88.8	<0.001*
SGPT (U/L)	77.3 ± 83.2	110.2 ± 88.2	0.001*
Ventilatory support	11 (10.5%)	105 (35.6%)	<0.001*
KRT indication			<0.001*
Metabolic acidosis	8 (10.5%)	73 (30.5%)	
Oliguria	45 (59.2%)	115 (48.1%)	
Anuria	1 (1.3%)	20 (8.4%)	
Raised renal parameters	22 (28.9%)	31 (13%)	
Other system involvement			<0.001*
Liver	27 (25.7%)	48 (16.3%)	
Lungs + Liver	32 (29.5%)	200 (67.5%)	

*: The asterisk indicates statistical significance, WBC: White blood cell count, SGOT: Serum glutamic oxalo acetic transaminase, SGPT: Serum glutamic pyruvic transaminase, KRT: Kidney replacement therapy

We identified a latency period of 1.28 days before the initiation of medical intervention, a phenomenon similarly reported in the existing literature.¹⁰ The factors linked to mortality align closely with those delineated in the current body of literature.¹⁰⁻¹²

Wang *et al.*¹³ and Hsu *et al.*¹⁴ have shown that CRRT would decrease mortality in patients of paraquat poisoning. Hsu *et al.* from Taiwan showed that early HP (< 4 hours) decreased mortality in 209 patients of severe paraquat poisoning.¹⁴ However, Yeh *et al.* from Taiwan showed that early HP or multiple sessions of HP do not decrease mortality.¹⁵

The volume of distribution of PQ is 1.2-1.6 L/Kg. The mean distribution half-life of plasma PQ is 5 hours, and the elimination half-life is 84 hours. PQ gets redistributed to organs and tissues within 4-5 hours of consumption and 82% gets excreted unchanged through the kidney in the first 48 hours, further slowly gets eliminated over days-weeks.¹⁶⁻¹⁸

Table 4: Multivariate analysis

Dependent variable	OR	p-value	95 % CI	OR	p-value	95 % CI
Latency of referral	0.927	0.017	0.870 - 0.896	-1.42 3	.001	-2.25 - -0.61
pO ₂	0.971	0.002	0.953 - 0.989	-6.742	<0.001	-1.16 - -3.34
Abnormal liver tests	0.857	0.141	0.698 - 1.053	1.270	.009	0.32 - 2.23

OR: Odds ratio, CI: Confidence interval

Table 5: Age-matched comparison between hemoperfusion and non-hemoperfusion

	Hemoperfusion	No Hemoperfusion	p value
Sex			
Males	60 (78.9%)	240 (74.1%)	0.377
Females	16 (21.1%)	84 (25.9%)	
Latency to first medical care (days)	0.96 ± 1.21	1.36 ± 1.23	0.010*
Latency to referral (days)	2.21 ± 2.32	3.49 ± 2.48	<0.001*
Serum creatinine (mg/dL)	2.82 ± 2.57	5.56 ± 3.37	<0.001*
Hemoglobin (gm/dL)	11.4 ± 1.31	11.71 ± 1.93	0.188
WBC (per mm ³)	12058.16 ± 3469.06	11984.85 ± 5318.43	0.909
Potassium (mEq/L)	4.08 ± 0.68	4.32 ± 0.76	0.010*
pO ₂	88.51 ± 14.76	83.91 ± 15.45	0.019*
Total bilirubin (mg/dL)	1.97 ± 1.64	4.4 ± 4.54	<0.001*
Direct bilirubin (mg/dL)	1.09 ± 1.22	2.53 ± 2.63	<0.001*
SGOT (U/L)	63.61 ± 52.59	98.76 ± 87.61	0.001*
SGPT (U/L)	68.97 ± 57.06	109.13 ± 92.13	<0.001*
Alkaline phosphatase (IU/L)	137.49 ± 110.71	141.02 ± 96.4	0.780
Anion gap	14.75 ± 3.92	15.06 ± 5.11	0.620
Ventilatory support	2 (2.6%)	114 (35.2%)	<0.001*
Other system involvement			<0.001*
Liver	4 (5.3%)	71 (21.9%)	
Lungs	0 (0%)	18 (5.5%)	
Lungs + Liver	68 (89.5%)	164 (50%)	
Mortality	54 (71.05%)	241 (74.38%)	<0.001*

WBC: White blood cellcount, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

The lungs and kidneys are primarily affected. The lungs uptake 10-20 times more PQ. Energy-dependent uptake by type 1 and type 2 alveolar epithelial cells causes elevated concentrations of the compound. Furthermore, the proximal tubular epithelial cells actively secrete PQ causing elevated concentrations in the renal tissues. Moderate to high PQ consumption causes redox reactions, releasing reactive oxygen species (ROS), resulting in pulmonary fibrosis. The underlying mechanism of PQ-AKI is only partly elucidated. It is thought to be due to recurrent redox reactions causing significant proximal tubular. Excess ROS production causes lipid peroxidation, inflammation, and cell death. Consumption of substantial quantities can lead to severe hepatocellular necrosis, damaging the liver. Heightened superoxide dismutase activity and diminished glutathione may cause severe liver necrosis. Given that PQ is primarily eliminated by the kidney, accumulation may occur in those with AKI, contributing to multi-organ failure.

PQ remains approved for use under the Insecticides/Pesticides Registered under section 9(3) of the Insecticides Act, 1968 for use in the Country (Jul 1, 2022). It is widely recognized that PQ poisoning leads to high death rates.

Therefore, the Government of India might start the ban on use according to Section 27(2) of the Insecticides Act, 1968. The government of Odisha introduced a prohibition on PQ and its derivatives in October 2024.

The volume of ingestion, delay in pursuing medical intervention, and the occurrence of multiorgan failure are linked to increased mortality. The availability of PQ should be regulated under stringent restrictions. Efforts to enhance education and awareness of PQ's toxicity and distribution methods should be intensified. If an alternative herbicide is accessible, the government may consider banning PQ.

Recent advances in PQ poisoning include anthrahydroquinone-2-6-disulfonate¹⁹, Edaravone²⁰ whose definitive roles are yet to be established in large studies.

The study had limitations – serum or urine PQ levels could not be estimated for the severity of poisoning due to a lack of resources. Follow-up after discharge to assess the long-term effects of PQ poisoning could not be done, and renal biopsy was not done in patients due to logistic and legal challenges.

To conclude, AKI may manifest in approximately one-third of cases involving PQ intoxication. An alarming mortality rate of 75% is observed in instances of PQ-AKI.

Conflicts of interest: There are no conflicts of interest.

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