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Original Article

Study on Clinical Profile and Treatment Outcome of Acute Paraquat Poisoning in an Intensive Care Unit in Bangladesh

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Abstract

Background: *Paraquat, one of the most widely used herbicides, is a major cause of self-harm related death in Bangladesh resulting from multiple organ failure. The primary objective aimed to identify the demographic & clinical characteristics of paraquat poisoning and the outcome of different treatment modalities.*

Materials and Methods: *A prospective observational study was conducted over twenty-four months at the Intensive Care Unit of Dhaka Medical College Hospital, a tertiary care referral hospital. Between March 2022 and March 2024, patients presenting with acute paraquat toxicity who fulfilled inclusion and exclusion criteriawere selected by purposive sampling. A total of 42 patients were enrolled in the study. Demographic, clinical, and treatment particulars were collected. The study evaluated the outcomes, including length of stay in the intensive care unit (ICU), the need for mechanical ventilation&hemodialysisandin-hospital mortality. SPSS version 25.0 was used for statistical analysis and reporting.*

Results: *Among the patients, 54.8% were men with a median age of 23.31 years residing in rural areas (85.7%). All cases were suicidal, primarily due to family disputes (40.5%) and personal relationship issues (21.4%). Symptoms included shortness of breath (40.5%), disorientation (28.6%), difficulty in swallowing (14.3%), vomiting (9.5%), and low urine output (7.1%). Most ICU admissions occurred after 24 hours post-ingestion (59.5%). Organ involvement included acute kidney injury (57.14%), acute respiratory distress syndrome (50%), hepatic impairment (14.3%), pulmonary fibrosis (14.3%), and septic shock (2.4%). Methylprednisolone was administered to 21 patients (50%), with an equal number also receiving methylprednisolone plus cyclophosphamide (50%). Only 10 (23.80%) patients received gastric lavage. The median ICU stay was 6 days (IQR 4-9), while the Median hospital stay was 8 days (IQR 1-12). In-hospital mortality was high, and 41 out of 42 patients (97.8%) died.*

Conclusion: *The rural population is mostly affected by paraquat poisoning for its easy availability,and clinical presentations, particularly pulmonary, renal and multi-systeminvolvement, are significantly associated with high mortality with the limited role of different treatment approaches.*

Keywords: Paraquat Poisoning, Suicidal Poisoning, Herbicide Poisoning, Acute Poisoning

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Introduction

Paraquat, the trade name of N,N -dimethyl-4,4 -bipyridinium dichloride, a viologen, was first described in 1882 by Weidel and Russo. 1933, Michaelis and Hill discovered its redox properties and called the compound methyl viologen. Brian et al. (1958), the scientists working for the British chemical company Imperial Chemical Industries (ICI), first described the herbicidal properties of paraquat. Naturally, after making this discovery, the company sought to produce and sell it for agricultural use.[1]

Soon after, in 1962, ICI began manufacturing a herbicide named Gramoxone using paraquat as the primary ingredient. Since Gramoxone was the first popular paraquat product, many still refer to paraquat as Gramoxone today.[1]

Paraquat is mainly formulated as an aqueous solution with surface-active agents. A low-strength granular formulation (also containing diquat) is available in some countries. Paraquat is a fast-acting, non-selective contact herbicide

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absorbed by the foliage with some translocation in the xylem. It is used for broad-spectrum control of broad-leaved weeds and grasses in fruit orchards and plantations and for inter-row weed control in many crops. It is also used for general weed control on non-cropland, as a defoliant on cotton and hops, for destruction of potato haulms, as a desiccant, and for control of aquatic weeds.[2]

In Bangladesh, according to Pesticide Technical Advisory Committee (PATC), Paraquat is recommended as a pesticide in tea, rubber, rice, and banana cultivation for killing sun grass, other grass, weeds (Dicot), etc. Paraquat is commercially available in Bangladesh as a bio-pesticide in 2 formulations – 20% paraquat and 20% paraquat plus 41% glyphosate combination. According to the Department of Agriculture Extension (DAE), 98 commercial brands of 20% Paraquat and 14 commercial brands of 20% Paraquat plus 41% Glyphosate combination are legally registered. Gramoxone, Paraxone, Squad 20SL, Fast Action 20 SL,Talfar 20 SL, Aroxon 20 SL, Cleanoxone 20 SL,Paratox 20 SL, Piquat 20 SL, Zero Herb 20 SLare some of the widely used paraquat brands in Bangladesh. As Paraquat is widely available in rural Bangladesh for its agricultural use, it has grown to be the major medium of self-harm over the years.[3]

Paraquat poisoning can manifest as acute and chronic toxicity. The major acute effects can result in both local and systemic manifestations. Local effects include ulceration of the skin, lips, tongue, pharynx, and esophagus. Systemic effects involve multipleorgan failure, including liver insufficiency, acute kidney injury, respiratory failure, and convulsions.[4]

After accumulation in the lungs, paraquat causes severe lung injury; it then manifests as oedema, haemorrhage, and interstitial inflammation, thus causing progressive fibrosis.

The exact mechanism of toxicity is not known completely. However, Paraquat releases free oxygen radicals (Superoxide and hydrogen peroxide) near the mucus membranes, resulting in mucosal damage in different organs and oxidative stress, which comprises lipid peroxidation, mitochondrial toxicity, oxidation of NADPH, activation of nuclear kappa B and apoptosis.[5-9]

Symptoms of Paraquat are initially vomiting, diarrhea, oropharyngeal burns, pharyngeal pseudo membranes, abdominal pain, and acute renal and hepatic insufficiency. Initial symptoms are followed by progressive pulmonary fibrosis and death within two to ten weeks.[10]

The Rationale of the Study

According to the World Health Organization (WHO), about 10,000 persons die by suicide per year in Bangladesh.[11]It is the fourth leading cause of overall injury-related deaths and the second important cause of injury-associated death in age groups of 20– 39 years in Bangladesh.[13]Though Paraquat poisoning is a major cause of deliberate suicidal self-harm in Bangladesh, data on clinical presentation, demographic characteristics, modes of treatments and outcomes of the patients in the Bangladeshi population are inadequate.[14] Mortality is an important issue in moderate to severe Paraquat poisoning patients. The mechanism of action of Paraquat is not completely known, but several methods have been used for its management. With the increasing incidence of mortality of Paraquat poisoning in the Intensive Care Unit (ICU) as well as in the medicine department of different hospitals in Bangladesh, adequate information on patients' demographic characteristics, clinical presentation and treatment outcomes needs to be evaluated.

Methodology:

Study Design: The research employed prospective morbidity, clinical course, treatments, and outcome of the patients presenting with paraquat poisoning. The observational study used a data collection form to collect data from the patients admitted tothe Intensive Care Unit at Dhaka Medical College Hospital, a tertiary-level medical facility, covering the period of 24 months from March 2022 to March 2024.Approval from the ethical review committee (ERC) was taken from the ERC of Dhaka Medical College after finalizing the study protocol.

Participant Selection: Patients more than 12 years of age, Paraquat poison taken orally, and Admission within 48 hours of PQ poisoning.

Patients with dermal or intravascular paraquat exposure, a combination of other types of poisoning, a history of severe diseases of the heart, lung, kidney, liver, or haematological system, Patients with multiple organ failure or cancer, Pregnant or lactating women, and Patients Who Were Readmitted from paraquat poisoning after initial improvement were excluded from the study. The analysis focused on relevant data, excluding individuals with suspected or undiagnosed conditions.

Evaluation Parameters: Demographic information, symptoms at the time of admission, physical examination results, and laboratory findings were thoroughly assessed. Additionally, the clinical course, treatments administered, and hemodialysis and ventilation requirements were scrutinized and compared regarding morbidity and mortality.

Variable Assessment: In the variable analysis, the data of patients diagnosed with paraquat poisoning were scrutinized to investigate their respiratory,renal, and hepatic involvement.

The focus was specifically on evaluating treatments involving pulse methylprednisolone alone versus cyclophosphamide plus pulse methylprednisolone. Additionally,the effects of antioxidants like N-acetyl cystine, Ascorbic acid, and Deferoxamine were evaluated, with other symptomatic and specific treatments disregarded.

Statistical Insights: In the scope of this evaluation, statistical data pertaining to the prevalence of ARDS and AKI among Paraquat poisoning werediagnosed according to Berlin criteria of ARDS and KDIGO definition of AKI, respectively. The frequency pulse methylprednisolone alone versus cyclophosphamide plus pulse methylprednisolone was analyzed, excluding consideration of other non-specific interventions. The prevalence of ARDS and AKI was determined, providing valuable statistical insights into the outcomes of patients within the studied population.

Statistical analysis:

Our study performed statistical analyses using the IBM SPSS 25.0 package program. The Kolmogorov-Smirnov test was used for normal distribution assessment. Categorical data were presented as frequency and percentage, mean and standard deviation if data is normally distributed, and median and interquartile ranges (IQR) if not normally distributed. In the statistical analyses, the Student t-test was used when the two groups were normally distributed; if the distribution wasabnormal, the Mann-Whitney U test was chosen. When the compared group is three or more, and it is normally distributed, a one-way ANOVA variance test was used, whereas, if the distribution is not normal, the Kruskal Wallis variance test was used. The statistical significance of the study was taken as $P < 0.05$.

Results:

Among the 42 patients studied, 54.8 % (n=23)were men, and the median age was 23.31 years with SD 7. 083.The majority of the patients were hailing from rural areas 85.7% (n=36) and were Muslims 85.7% (n=36). Regarding occupation of the cases, 33.3 % (n=14) were students, followed by 21.9 % (n=9) housewives, 11.9% (n=5) related to businesses, and 9.5% (n=4) farmers. All cases were suicidal.

Family disputes (40.5%, n=17), followed by personal relationship issues(21.4 %, n=9), were reported as the primary reason for paraquat poisoning.

From the available records, 3 cases (7.14 %) had comorbid conditions. Approximately 10% of the study population reported having an underlying psychiatric illness, and 2 (4.8%) patients reported previous suicide attempts.

Table 1. Socio-demographic & clinical characteristics of paraquat poisoning patients

		n (%)
Gender	Male	23 (54.8)
	Female	19 (45.2)
Age, years	<18	8(19.04)
	18–30	26 (61.92)
	30-45	8 ((19.04))
Religion	Muslim	36 (85.7)
	Hindu	6 (14.3)
	Christian	0
Residence	Rural	36 (85.7)
	Urban	6 (14.3)
Presentation to hospital	Direct	5 (11.90)
	Referral	37(88.10)
Marital status	Married	14 (33.3)
	Unmarried	25 (59.5)
	Divorced	2 (4.76)
	Widowed	1 (2.4)
Reason for paraquat ingestion	Suicidal	42(100%)
	Family disputes	17 (40.50)
	Personal relationship issue	9 (21.4)
	Depression	5 (11.90)
	Financial issue	2(4..76)
	Academic failure	4 (9.5)
	Unemployment	2(4.76)
	Unknown	3(7.14)
Comorbidities	Cardiac disease	1 (2.4)
	DM	1(2.4)
	Psychiatric illness	1 (2.4)
Previous suicidal attempts	Previous suicidal attempts	2 (4.8)
Symptom at presentation	Vomiting	4 (9.5)
	Shortness of breath	17(40.5)
	Low urine output	3 (7.1)
	Disorientation	12 (28.6)
	Difficulty in swallowing	6 (14.3)
Time interval between paraquat ingestion and ICU admission	Within 6 hours	1 (2.4)
	Within 24 hours	16 (38.1)
	After 24 hours	25 (59.5)

Common symptoms included shortness of breath (40.5%), disorientation (28.6%), difficulty in swallowing (14.3%), vomiting (9.5%), and low urine output (7.1%). Most patients were admitted to the ICU more than 24 hours post-ingestion (59.5%), with only 2.4% within 6 hours (Table 1).

Organ involvement included acute kidney injury (57.14%), acute respiratory distress syndrome (50%), hepatic impairment (14.3%), pulmonary fibrosis (14.3%), and septic shock (2.4%) (Figure 1).

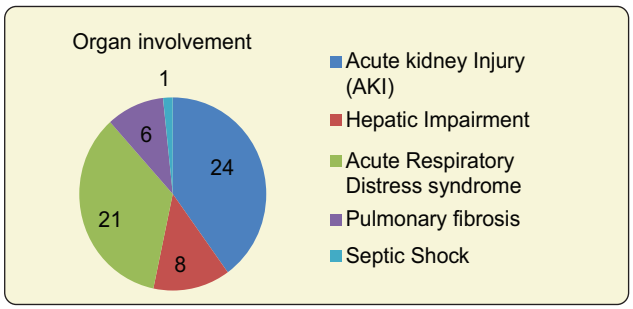

Figure: 1 Organ involvement in acute paraquat poisoning patients (n, N=42)

This data underscores the range and severity of complications from paraquat poisoning, highlighting the necessity for prompt medical care.

Table 2. Baseline & Endpoint vital signs and oxygen measurements by

Attribute	Mean ±SD / Median (IQR)	
	Baseline	Endpoint
Pulse	131.06 ± 18.18	131.7 ±39.31
Systolic blood pressure	126.11 ±24.52	120 ±23.94
Diastolic blood pressure	81.67 ± 18.86	76.87 ±17.78
Respiratory rate	34.5 ±7.17	34.81 ±11.96
Temperature	97.88 ±0.48	100.3 ±1.29
SpO_2	86.50 ±4.99	84.62 ±9.38
FiO_2	38.94 ±16.31	131.7 ±39.31

Baseline and endpoint vital signs reveals there were no statistically significant differences vital signs or oxygen measurements, including pulse rate, systolic and diastolic blood pressure, respiratory rate except high temperature, and FiO2 in endpoint (Table 2).

Table 3. Baseline & Endline acid-base and respiratory parameters

Attribute	Mean ±SD / Median (IQR)	
	Baseline	Endline
pH	7.2 ±0.7	6.7 ± 0.9
Bicarbonate	18.6 ± 2.9	13.1 ±3.6
PaO_2	65.1 ±17.9	54.9 ±15.3
$PaCO_2$	33.4 ±8.9	31.0 ±5.3

PH was significantly lower in the endline (6.7±0.9) compared to the baseline (7.2±0.7). Similarly, at endline, the Bicarbonate level was significantly lower in the endline (13.1 ±3.6) compared to the baseline (18.6±2.90) (Table 3).

Table 4. Baseline and endline blood and renal profile

Attribute	Mean ±SD / Median (IQR)	
	Baseline	Endline
Serum Creatinine (mg/dl)	2.54±2.50	6.54 ±9.09
Hemoglobin (g/dl)	11.8±1.8	8.12 ±2.03
WBC count (x 1000/mm^3)	12.07±2.8	19.56 ±9.91
Platelet count (x 1000/mm^3)	231.89±13.32	135.18 ±66.19
Serum ALT (U/L)	183.52±60.13	191.23±62.76

Serum creatinine was significantly higher in endline (6.54 ±9.09) compared to baseline (2.54 ±2.50). At endline, the hemoglobin level was significantly lower in the (8.12 ±2.03 g/dl) compared to the baseline (11.8 ±1.8 g/dl) (Table 4).

Methylprednisolone was administered to 21 patients (50%), with an equal number also receiving methylprednisolone plus cyclophosphamide (50%).

Table 5. Treatment received (N=42)

Treatment / Intervention	n (%)
Gastric lavage	10 (23.80)
Methylprednisolone	21 (50)
Methylprednisolone plus cyclophosphamide	21 (50)
Ascorbic Acid	30(71.42)
N- Acetyl cysteine	0
Deferoxamine	0
Hemodialysis	14 (33.33)
Mechanical ventilation	21(50)

Only 10 (23.80%) patients received gastric lavage. Ascorbic acid was given to 30 patients (71.42%), while none received N-acetyl cysteine. Hemodialysis was performed on 14 patients (33.33%), and mechanical ventilation was used for 21 patients (50%). (Table 5)

Table 6. Outcome

Attribute	Mean ±SD / Median (IQR)
ICU length of stay in days	6 (IQR 4-9)
Hospital length of stay in days	8 (IQR 1-12)
	n (%)
In hospital mortality	41 (97.8%)

The median ICU length of stay was 6 days, with an interquartile range (IQR) of 4 to 9 days. The median hospital length of stay was 8 days, with an IQR of 1 to 12 days. The in-hospital mortality rate was notably high, with 41 out of 42 patients (97.8%) succumbing to the poisoning (Table 6).

Discussion:

Acute poisoning cases in the developing world are positively associated with male gender young age with suicidal intent. In this study, 54.8% (n=23) were men, with a median age of 23.31 years (SD 7.083). Most patients were from rural areas (85.7%, n=36) and were Muslims (85.7%, n=36). According to a retrospective cohort study on the epidemiology of suicide in Bangladesh the rate of suicide was found to be 17-fold higher (95% CI 5.36-54.64) in the rural population compared to urban rates.[15]Regarding occupation, 33.3% (n=14) were students, 21.9% (n=9) were housewives, 11.9% (n=5) were business-related, and 9.5% (n=4) were farmers. All cases were suicidal, with family disputes (40.5%, n=17) and personal relationship issues (21.4%, n=9) as primary reasons. Most pesticide poisoning cases in this study had socio-environmental stressors like other poisoning cases worldwide.[15] Clinical characteristics showed symptoms like shortness of breath (40.5%), disorientation (28.6%), difficulty in swallowing (14.3%), vomiting (9.5%), and low urine output (7.1%). Most ICU admissions occurred more than 24 hours post-ingestion (59.5%), with only 2.4% within 6 hours. Organ involvement included acute kidney injury (57.14%), acute respiratory distress syndrome (50%), hepatic impairment (14.3%), pulmonary fibrosis (14.3%), and septic shock (2.4%). Initial presentation with acute kidney injury and late development of pulmonary fibrosis is observed in several case reports in acute paraquat poisoning in Bangladesh.[16]

Recognizing paraquat poisoning and providing initial first aid isthe cornerstone of effective management. The primary challenge in acute paraquat poisoning cases is making decisions regarding airway and ventilation. If the patient is conscious and not vomiting, gastric lavage with activated charcoal (1–2 g/kg) or Fuller's earth (1–2 g/kg) should be performed. This helps decontaminate the stomach and prevent further absorption of the toxin.[4]The use of gastric lavage without administration of an adsorbent has not shown any clinical benefit and should be avoided.[17] But confirmatory test plasma and urine sodium dithionate tests and availability of activated charcoal for gastric decontamination is lacking in Bangladesh perspective even in tertiary care setting. All patients in the study were diagnosed with paraquat poisoning on the basis of history and circumstantial evidence and no patient received gastric decontamination by activated charcoal due to its unavailability.

The development of type 2 respiratory failure may be an early predictor of ARDS in patients with worse outcomes. ABG analysis of the patients reveals deterioration of acidosis as well as hypoxemia in most patients; 21 of them developed ARDS.Limiting FiO2 to a minimum to maintain PaO2 of about 60–65 mm Hg or SpO2 88–90% may be of some hypothetical mortality benefit.A recent retrospective cohort study by *Lin et al., 2021* supports the hypothesis.[18] Usually, patients who get intubated for respiratory failure have a stormy course and deteriorate rapidly in a few hours to days. In our study, 21 (50%) patients received mechanical ventilation, and all of them died subsequently.

AKI is common following paraquat ingestion, and certain clinically useful variables such as acute hepatitis, the time to hospital arrival, Severity Index and Plasma Paraquat (SIPP) score and PaO2 at admission are powerful predictors of AKI.[19]In this study, 25 (59.5%) patients were admitted to ICU 24 hours after paraquat ingestion, mean baseline SPO_2 was 84.62 ±9.38 %.24 (57.14%) patients in this study developed AKI. Hemodialysis was given in 14 (33.33%) patients.

Paraquat toxicity is primarily due to oxidative stress,[20] leading to suggestions for antioxidant and anti-inflammatory treatments. However, no strong evidence supports the use of vitamin C or N-acetylcysteine.[21-24] Anti-inflammatory pulse therapy is debated, with mixed results from different studies.[25] A recent Cochrane Review indicated that glucocorticoids with cyclophosphamide may slightly reduce mortality in paraquat-poisoned patients but showed no significant long-term benefit, with conclusions limited by variability and imprecision.[26] The infection risk associated with this combination remains unclear. Other drug combinations also lack supportive evidence. In this study, pulse methylprednisolone, pulse methylprednisolone and cyclophosphamide combination were used, but both groups of patients failed to show any significant morbidity or mortality benefit. The median length of stay of the study population at ICU was 6 days (IQR 4-9) with 97.5% overall mortality.

The majority of the population in rural Bangladesh are dependent on agriculture. Due to wide availability of paraquat pesticides and lack of urgent primary care in rural areas has led to an increased rate of case fatality in acute paraquat poisoning.

A recent article made headline in a national newspaper in Bangladesh titled – "Every day 175 poisoning patients come to hospital in Bangladesh" regarding the huge burden of suicide-related death in Bangladesh, accounting for about 10 to 14 thousand deaths annually, among which paraquat poisoning has the highest mortality rate.[27]

Legislative regulation restricting the use of pesticides, particularly paraquat, can significantly impact the overall suicide burden. Additionally, enforcing measures for the safe storage and proper use of paraquat, along with implementing safety protocols, is essential. Between 1996 and 2007, Bangladesh's regulatory authorities partially or fully banned 21 pesticides, leading to a transition towards less hazardous WHO toxicity class II, III, and U pesticides. All WHO Class I highly hazardous pesticides (HHPs) were prohibited in 2000. This ban reduced hospital mortality from pesticide poisoning, with rates decreasing from 15.1% to 9.5%, a relative reduction of 37.1%, without any noticeable decline in agricultural productivity.[28] Similar effects were observed in Europe, Malaysia, Sri Lanka, and Korea after the ban on paraquats. [29-30]So, Appropriate actions need to be taken in Bangladesh to reduce the burden of high mortality of paraquat poisoning.

Regulating access to these highly hazardous pesticides with a national ban is time-consuming. Knowledge of biological solutions and other environmentally friendly, non-pesticide, and economically viable agricultural methods may help in the long run.

Limitations of the study:

The diagnosis of paraquat poisoning was based on history and clinical findings; a qualitative or quantitative confirmatory test, such as a plasma or urine dithionate test, was not done.

Moreover, the absence of a control group and the lack of a comparative analysis with different treatment modalities may impede the study's capacity to formulate definitive conclusions on the effectiveness of treatment modalities.

Conclusion:

In conclusion, this study of paraquat poisoning cases in Bangladesh provides valuable insights into the clinical profile, treatment outcomes, and management approaches. High mortality with different treatment approaches emphasizes the need to restrict the use of paraquat poisoning and look for safer alternative pesticides for agricultural use. High fatality warrants the need for further research to formulate effective treatment.

Ethical Measures:

After finalizing the study protocol, approval from the ethical review committee (ERC) of Dhaka Medical College was obtained. Informed written consent was obtained from the patient or legal guardian of the patient who was unable to communicate properly. To safeguard confidentiality and protect anonymity, each patient was given a special ID number, which was followed in each step of data collection, editing, storage, and analysis.

Recommendation:

Paraquat has a long history of existence. However, its agricultural and commercial success is deemed naughty by its fatal outcome, even with mechanical ventilation or hemodialysis support when used as a method of deliberate self-poisoning. So, it is high time to restrict its access, storage, use, or ban it and shift to safer alternative herbicides for agricultural purposes.

Conflict of Interest:

The authors have no conflict of interest to declare.

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