Clinical Profile of Paraquat Poisoning - A Case Series

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ABSTRACT

Introduction : Paraquat is a non-selective contact herbicide which is highly toxic to humans. On ingestion it can cause ARDS, rapidly progressive pulmonary fibrosis, multi organ dysfunction and is associated with a high mortality.

Objective : To study the clinical features, complications, treatment modalities and their outcome in patients of paraquat poisoning admitted in a tertiary care centre.

Materials and Methods : Twelve cases of paraquat poisoning at a tertiary care centre in central India were studied over a period of 12 months. All of them were treated with gastric lavage using activated charcoal, steroids and antioxidants. Supportive care in the form of haemodialysis or peritoneal dialysis was provided, whenever necessary. The patients were observed for the development of various complications.

Results : The mortality (10 out of 12) was very high. Two patients died within 48 hours of consumption. All the patients developed oropharyngeal ulcerations. Eleven patients developed multi organ dysfunction. Ten developed acute kidney injury with metabolic acidosis. Hepatic involvement was seen in eight patients whereas six had pulmonary manifestations.

Conclusion : Paraquat is highly toxic to humans and is almost always fatal even with minimal exposure. With the current modalities of treatment and with no antidote available, mortality remains high.

Key words : Paraquat, Pulmonary fibrosis, Multi organ dysfunction

Introduction:

Paraquat (N, N' - DIMETHYL - 4,4' - BIPYRIDINIUM DICHLORIDE) introduced in 1962 is an organic compound with chemical formula [(C6H7N)2] Cl2 belonging to a group of dipyridyl herbicides. It is a non-selective contact herbicide widely used in Asia but banned in European Union and is under restricted use in USA. It has low environmental toxicity due to rapid deactivation upon soil contact.[1] With no specific antidote available it is highly toxic to humans and can cause both local and systemic effects. Diquat is another example of dipyridyl herbicides. Paraquat is different from diquat as it is selectively accumulated in the lungs causing pneumonitis and fibrosis. Toxicity most commonly occurs after oral ingestion and may be mild (ingestion of < 20 mg paraquat ion/kg body weight) to fulminant (>40 mg paraquat ion/kg body weight), with the latter having poor outcomes.[2]

It causes intense local irritation of the skin, lips, tongue, pharynx and the oesophagus, multiple organ (cardiac, respiratory, hepatic and renal) failure may occur, although pulmonary features are the usual cause of death.[2]

GI Decontamination (with Fuller's Earth or activated charcoal) and the administration of adsorbents and extra corporeal elimination techniques remain the mainstay of treatment.

Aims and Objectives :

1. To study the clinical manifestations and the complications of paraquat poisoning patients admitted in a tertiary care centre in central India.
2. To the study the outcome of paraquat poisoning patients with the current modalities of treatment

Materials and Methods :

Twelve patients of paraquat poisoning admitted to a Tertiary Care Centre in Central India between November 2018 to November 2019 were studied. The diagnosis was made upon the obtained history,

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Received on 18th December 2019 Accepted on 27th December 2019

reference letters and the bottle produced. Treatment histories from other hospitals were obtained as per the reference letter.

Upon arrival, patients were stabilised by securing airway, breathing and circulation. Gastric lavage was given using normal saline (5ml/kg of body weight) and activated charcoal (1gm/kg) immediately after admission. All the patients underwent the following tests at admission: renal function test, liver function test, prothrombin time, arterial blood gas analysis, chest X-ray. Adequate hydration was ensured. Steroids (Injection Dexamethasone 4 mg IV 6 hourly for 3-5 days) and Antioxidants (Vitamin C 500 mg BD and Vitamin E 400 mg BD) were given to all patients. Renal and liver function tests were repeated on every alternate day.

Patients were monitored for development of respiratory distress as evidenced by tachypnoea or a fall in PaO2 < 70 mmHg on arterial blood gas analysis at room air. Renal dysfunction was defined as per KDIGO clinical practice guidelines for acute kidney Injury. Hepatic dysfunction was taken as more than double fold rise in transaminases and/or INR >1.5. Involvement of $\geq$ 2 organ systems were defined as having multi organ dysfunction. Supplemental oxygen was given at the lowest possible concentration required to maintain adequate tissue oxygenation. Dialysis support was given only if indicated i.e. symptomatic uraemia andacidosis, hyperkalaemia, oliguria and volume overload.

Results :

Patient characteristics are enlisted in ***Table 1.*** Age of patients ranged from 14 to 34; nine men and three women. The degree of poisoning was assessed by number of mouthful (20 ml) of paraquat concentrate ingested i.e. < 1 mouthful as mild, 1 mouthful as moderate and 2 or more as severe. Young males comprised most of the patients. Ten patients had moderate to severe poisoning. Due to lack of facility, plasma paraquat levels or urine dithionite test were not done. Only one patient was admitted within 6 hours of paraquat ingestion. Soon after ingestion, all the patients developed vomiting and burning sensation in the mouth. Specific treatment in the form of steroids and antioxidants were given to all the patients. Inspite of the treatment, most of the patients developed renal, hepatic and respiratory dysfunction.

Two patients with oral exposure to paraquat survived and the amount of exposure in the both the cases was mild, one of them developed AKI which recovered spontaneously without dialysis.

The commonest symptoms were oral ulceration, dysphagia and vomiting followed by yellowish discolouration of eyes and urine and dyspnoea. All the patients had oropharyngeal excoriations and coated tongue at the time of presentation. Ten patients developed acute renal failure with a mean peak serum creatinine of 6.8 mg/dl. Six patients were given dialysis support (HD in 1 and PD in 5).

Respiratory failure was seen in six patients whereas eight patients had features of hepatic dysfunction. Eleven patients had multi organ failure. The overall mortality was 83%. Multi organ involvement and respiratory failure were the main causes of mortality. Survival period ranged from 24 hours to 19 days.

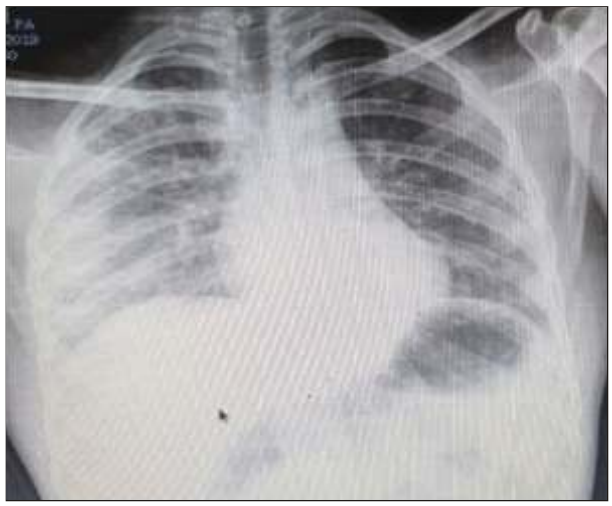

Figure 1 : **Chest X-ray suggestive of Pulmonary opacities in a paraquat poisoning patient taken at the time of admission, 3 days post consumption.**

Table 1 : **Patient Characteristics**

Sr. No.	Age / Sex	Route of Exposure	Severity of Poisoning	Time to receive first medical attention	Treatment received	Complications	Outcome (Survival/Death)
1	34/M	Oral	Severe	12 hours	GL/PD/ST/ AOT	Oro pharyngeal excoriation at presentation, AKI (non-oliguric) and Hepatic Dysfunction on Day 2	Death (19 days)
2	18/M	Oral	Moderate	36 hours	GL/PD/ST/ AOT	Oro pharyngeal ulcers, Painful dysphagia at presentation, AKI (Oliguric) and Hepatic Dysfunction on Day3, Respiratory distress on Day 5	Death (11days)
3	26/M	Oral	Severe	8 hours	GL/PD/ST/ AOT	Oro pharyngeal ulcers and Painful dysphagia at presentation, AKI (oliguric) on Day2, Hepatic Dysfunction on Day3	Death (17 days)
4	18/M	Oral	Severe	10 hours	GL/PD/ST/ AOT	Oro pharyngeal ulcers at presentation, AKI (oliguric) on Day1, Hepatic Dysfunction on Day 3	Death (13 days)
5	22/M	Oral	Mild	16 hours	GL/ST/AOT	Oro pharyngeal ulcers at presentation	Survival
6	28/F	Oral	Severe	8 hours	ST/AOT	Oro pharyngeal ulcers at presentation, AKI (oliguric) on Day1, Respiratory distress on Day1	Death (2 days)
7	25/M	Oral	Moderate	72 hours	HD/PT/ST/ AOT	Oro pharyngeal ulcers at presentation, AKI (non-oliguric) on Day 3, Hepatic Dysfunction on Day 4, Respiratory distress on Day 4	Death (10 days)
8	18/F	Oral	Severe	4 hours	GL/ST/AOT	Oro pharyngeal ulcers, Painful dysphagia, Epigastric Pain, AKI (oliguric) and Respiratory distress on presentation	Death (1 day)
9	18/M	Oral	Severe	14 hours	GL/ST/AOT	Oro pharyngeal ulcers at presentation, AKI (non-oliguric) and Hepatic Dysfunction on Day 3, Respiratory distress on Day 6	Death (16 days)
10	14/M	Inhala-tional	-	96 hours	ST/AOT	Oro pharyngeal ulcers at presentation, Hepatic Dysfunction at presentation & Respiratory distress on Day 6	Death (15 days)
11	24/F	Oral	Mild	7 hours	GL/ST/AOT	Oro pharyngeal ulcersat presentation, AKI (non-oliguric) on Day 3	Survival
12	28/M	Oral	Severe	22 hours	GL/ST/AOT	Oro pharyngeal ulcers at presentation, AKI (oliguric) & Hepatic Dysfunction on Day 3	Death (9 days)

GL : Gastric Lavage (using Activated Charcoal); PD : Peritoneal Dialysis; HD : Haemodialysis; ST: Steroid Therapy;
AOT : Antioxidant Therapies; AKI : Acute Kidney Injury (KDIGO Guidelines); All time parameters are with respect to consumption.

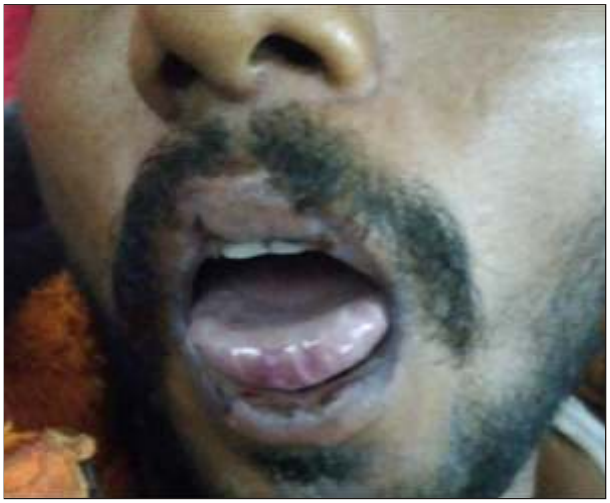

Figure 2 : **Coated tongue in a paraquat poisoning patient on admission**

Discussion :

Exposure to paraquat can be due to intentional ingestion or occupational exposure, e.g. Inhalational, dermal and eye contact. A dose of 3-6 g is fatal for adults.[1] So, even a small sip of paraquat may be lethal. Paraquat is a water-soluble quaternary ammonium derivative. It is poorly absorbed by the oral route in humans. Around 1-5% of an oral dose is absorbed in the gut. The volume of distribution is 1-2 L/kg.[3] It is unbound to plasma proteins. Plasma paraquat concentration exhibits a mean distribution half-life of five hours and a mean elimination half-life of 84 hours.[3]

Mechanism of toxicity :

Paraquat induced toxicity is a manifestation of redox cycling and generation of reactive oxygen species like superoxide anions which may react to form hydrogen peroxide and the highly reactive hydroxyl radical, which in turn is responsible for lipid peroxidation and cell death. Depletion of nicotinamide adenine dinucleotide phosphate with bound hydrogen ion (NADPH), is the second contributing factor as both paraquat redox cycling as well as hydrogen peroxide detoxification via glutathione are NADPH dependent.[4] Other secondary effects of oxidative stress also play synergistic effect in the manifestation of overall clinical presentation of paraquat poisoning. These are lipid peroxidation,[5] mitochondrialtoxicity,[6] oxidation of NADPH,[7] activation of nuclear factor kappa beta,[8] and apoptosis.[9]

Clinical Features :

Generation of highly reactive oxygen and nitrogen species results in damage to most organs but the toxicity is particularly severe in the lungs as it is taken up against a concentration gradient in lungs.10In the lungs, initially it causes acute alveolitis and ARDS (Acute Respiratory Distress Syndrome) in one to three days and subsequently progresses to rapidly progressive fibrosis.

Of the six patients who developed pulmonary complications, two of them were symptomatic within 24 hours of consumption and it was associated with a fulminant course culminating in death within 48 hours. The other four patients had pulmonary complications which manifested over a period of 1 week, all invariably leading to Type 1 Respiratory Failure and Death. Chest Xray in all such patients was suggestive of pulmonary fibrosis ***(Figure 1).***

Paraquat is eliminated mainly by the kidney and acute kidney injury (AKI) is a recognized complication of paraquat poisoning, with reports of both oliguric and non-oliguriccases.[11,12] In this series, ten patients developed renal manifestations, six being oliguric. The mechanism of renal damage is likely to be related to redox cycling and oxygen toxicity. Histopathological examination of a fatal case of paraquat poisoning revealed proximal tubular necrosis whereas glomerular and tubular haemorrhage have been described in cases of transient oliguria.[13] Paraquat poisoning may lead to a Fanconi syndrome with a variety of proximal tubular abnormalities, including glycosuria, phosphaturia and aminoaciduria.[14] The precipitation of acute renal failure is mostly multifactorial. Late referral, significant GI fluid losses, circulatory failure, multi-organ failure and septicemia are the commonly encountered precipitating factors. Fluid replacement is an immediate clinical priority to prevent worsening of renal functions due to hypovolemia.

After ingestion, paraquat can cause burns and haemorrhagic ulcerations of the gastrointestinal (GI) tract. All the patients in this case series had oropharyngeal excoriations leading to dysphagia and a coated tongue which is termed as paraquat tongue ***(Figure 2).*** Ocular exposure can result in protracted opacification of the cornea. The patients may also exhibit a transverse band of white discoloration of the nail plate, a recognized feature of paraquat poisoning.[15] Dermal contact can cause dermatitis. Paraquat is well absorbed from injured skin and severe systemic toxicity with fatal outcomes after dermal exposure had been reported.[16.17] For the neurological system, paraquat causes cerebral oedema due to its direct toxicity on cerebral blood vessels and indirectly the hypoxiasecondary to pulmonary damage. Other toxic effects of paraquat include ventricular arrhythmias, hypotension and cardio-respiratory arrest. The major cause of death is due to respiratory failure.

Investigations and Management :

Airway management and adequate ventilation are very important as patients with paraquat poisoning may develop airway obstruction due to oropharyngeal ulceration and oedema. All our patients had their airway secured upon arrival at the Emergency Medical Services (EMS). However, since high concentrations of oxygen (O2) are contraindicated as they increase the formation of free radicals in the redox cycling of paraquat, the lowest O2 level possible to limit tissue hypoxia was used. The most important prognostic indicator is the amount of paraquat absorbed.[10] Blood paraquat assay can be done to predict survival.[18] The urine dithionite test is useful to estimate the level of exposure but is not accurate as urine paraquat excretion depends on renal function. Paraquat reactswith dithionite to form a stable blue radical ion.

Extracorporeal elimination techniques, such as haemodialysis / hemoperfusion, have been used widely in paraquat poisoning. However, paraquat is not dialyzable effectively. These techniques probably do not increase the survival rate because the potentially lethal concentration of paraquat may have already been attained in the highly vascular tissue of vital organs and in the pneumocytes when these techniques are initiated.[19]

Paraquat has no proven antidote. Some authors advocate routine use of antioxidants (Vitamin C 4000 mg/day and Vitamin E 250 mg/day) to prevent free radical injury, however with unproven efficacy.[10,20] Pulse therapy using steroid (methyl prednisolone or dexamethasone) and cyclo phosphamide has been shown to be effective in preventing pulmonary fibrosis in some studies.[21,22] All our patients received steroids and anti-oxidants but eleven out of twelve of them still developed multi organ dysfunction. Deferoxamine by iron chelation and decreasing the formation of hydroxyl radical and NAC by maintaining the intracellular glutathione levels may protect against the toxicity of paraquat.[23,24]

Recently the use of Nitric Oxide has also been a subject of interest. Paraquat specific IgG antibodies and their Fab fragments are effective but the "window of opportunity" is very short, only a few hours at the most.[25] Lungtransplantation has been performed in a few patients.[26]

Conclusion :

Paraquat poisoning carries a very high mortality. Even small quantities of paraquat in spite of early medical intervention can have a fulminant course. The current modalities of treatment are largely ineffective and without the availability of any specific antidote, the mainstay of treatment is supportive the cause of death remains acute respiratory distress syndrome, progressive pulmonary fibrosis and hepatorenal failure. Recognizing the clinical presentation and getting history of exposure, early administration of gastric adsorbents (activated charcoal or fuller's earth) and activated charcoal hemoperfusion may have a critical role in preventing irreversible pulmonary damage and multi organ failure.

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