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Original Research Article

Spectrum of Clinical Manifestations of Paraquat Poisoning In Rural Children of West Bengal Admitted At Tertiary Care Hospital

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Abstract

Objective: The clinical characteristics and experience of rural Indian children of West Bengal with paraquat poisoning – a retro prospective analysis. ***Methods:*** The study: From June 2014 through April 2019, fourteen children with paraquat poisoning who presented to the hospital were enrolled .The collected clinical indices of these cases were and analyzed. ***Results:*** oral ingestion of paraquat were found in most of the children and the commonest route of poisoning. Different degrees of damage were found in multiple systems in their bodies. Initial therapy consists of removing the paraquat from the body (decontamination) and preventing further absorption for oral exposures by using activated charcoal followed by pulse therapy using methylprednisolone (20 mg/kg/d×3d) and Gamma globulin (total 2 g/kg divided into 3 d to 5 d)for all children in the early stage. Prednisone was then given orally for 4wk to 8 wk. The total mortality rate of the patients was 64.8% (09 of 14 patients died). Statistical differences ($P<0.05$) were found between the surviving and dead patients, with regard to age, plasma paraquat levels, the highest levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, total bilirubin, direct bilirubin, indirect bilirubin, blood urea nitrogen,creatinine and pH value, the lowest levels of PaO2, PaCO2 and SaO2. Plasma paraquat level was positively related to pH value, but was negatively related to PaO2, PaCO2 and SaO2 levels. Hepatic and renal complications are encountered in admitted patients but the patients survived.However the fibrosis of the lung is one of the dreaded complications in the long run. ***Conclusions:*** There is no cure for Paraquat poisoning. In this study, pulmonary fibrosis was the primary cause of death.Treatment by administering pulse doses of methyl prednisolone and Gamma globulin seems to be effective in the early stage. However, the treatment may not reverse the development of pulmonary fibrosis. The long-term prognosis of paraquat poisoning was not optimistic.For predicting the prognosis, plasma paraquat level is significant.

Keywords: Poisoning Paraquat Methyl prednisolone.

INTRODUCTION

Paraquat (1, 1' – dimethyl-4, 4'-bipyridinium) was first produced for commercial purposes in 1961. Worldwide, paraquat is still one of the most commonly used herbicides. It is a widely used contact herbicide with a good safety record when used properly. People could be poisoned through skin contact, respiratory tract, oral ingestion and other causes It came into disrepute because of accidental or intentional ingestion leading to a high mortality. Paraquat toxicity can produce both local and systemic effects. The major acute effects are the ulceration of skin, lips, tongue, pharynx and esophagus. The acute systemic effects are usually pulmonary edema, cardiac, renal or hepatic failure and convulsions. Treating paraquat poisoning is very difficult because no specified antidotes exist. The mainstay of treatment remains the gastric lavage and the administration of adsorbents and extracorporeal elimination of paraquat, though the clinical efficacy remains controversial. The data on paraquat poisoning from our country is scant. This study aimed to investigate the clinical characteristics with paraquat poisoning and in hospitalized children.

MATERIALS AND METHODS

Fourteen children with paraquat poisoning who were hospitalized in Calcutta National Medical College from June 2014 through March2019 were included in this study. The clinical indices of these children were collected and retrospectively analyzed. The diagnosis was based on the history and the verification of the ingested herbicide which were brought by the caregivers. Immediately after admission, gastric lavage was done using tap water (5ml/kg of body weight) and activated charcoal (1gm/kg dissolved in 250- 400 ml of tap water) was given as an adsorbent. Adequate hydration was ensured by CVP monitoring using jugular canulation and keeping CVP of 8 – 10 cm

of saline. To prevent free radical injury and lung fibrosis, steroids (injection methyl predisolone 20 mg/kg/d IV for 3- 5 days) and gammaglobulin (total 2g/kg divided in 3-5 days) were given to all patients. Supplemental oxygen was administered only when arterial oxygen tension decreased to <50 mmHg and / or the patient had symptoms of respiratory failure. Respiratory failure was diagnosed if mechanical ventilation was used to treat hypoxia not corrected by supplemental oxygen delivered by nasal canula or facemask. Dialysis support was given only if indicated for acute renal failure i.e. symptomatic uremia and acidosis, hyperkalemia or volume overload. Data with normal distribution were expressed as mean ± standard deviation and were statistically analyzed. P value<0.05 was considered to be statistically significant.

RESULT

The 14 patients comprised 12 boys and 2girls whose ages ranged from 10 mo to 12 y (6.84±3.81y). All children were poisoned by taking paraquat orally. Two children were poisoned by licking empty bottles of paraquat. The other children ingested paraquat to commit suicide with a maximum dosage of 20 mL. The length of hospital stay was 7 d to 24 d. The time that elapsed from paraquat ingestion to hospitalization was within 24 h, except for an 11-y-old girl who was admitted into hospital 6 d after poisoning because of the concealment of paraquat ingestion. The patients showed various types of symptoms (Table 1).Five children had leucocytosis with white blood cell (WBC) count of 10.21×109/L to 20.99×109/L (14.89± 3.31×109/L). Three children had normal WBC count of 4.56×109/L to 6.39×109/L (7.82±1.63×109/L). One child had leucopenia with a WBC count of 3.47×109/L. Seven children had microscopic hematuria (BLD1+~3+). Five children had proteinuria (PRO1+~2+) simultaneously. The plasma paraquat levels ranged from 0.01 μg/mL to 14.02 μg/mL (5.39±4.68 μg/mL).Seven patients had hepatic and renal function injuries.The serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), blood urea nitrogen (BUN) and creatinine (Cr) levels of these patients increased within 3 d after poisoning. These indices reached the peak within 7 d to 10 d as follows: ALT (56U/L to 469U/L, mean 203.27±113.23U/L), AST (46U/L to 587U/L, mean 155.05±134.89U/L), GGT (41U/L to 286U/L, mean 134.40 ± 78.01U/L), TBIL (23 μmol/L to151.7 μmol/L,mean 72.28±42.93 μmol/L), DBIL (9.1 μmol/L to 105.9 μmol/L, mean 50.38±31.71 μmol/L), IBIL (5 μmol/Lto 45.8 μmol/L, mean 21.90±12.73 μmol/L), BUN(11.71mmol/L to 40.09 mmol/L, mean 26.10±7.89 mmol/L),Cr (108 μmol/L to 773 μmol/L, mean 307.80±220.31 μmol/L).These indices of patients with hepatic and renal function injuries improved after reaching the peak, except for one patient who abandoned therapy. None of the patients died from hepatic or renal complications.Five children exhibited electrolyte disturbance, including hypokalemia (2.20 mmol/L to 3.49 mmol/L, mean 3.08±0.41 mmol/L), hyponatremia (119 mmol/L to 133 mmol/L, mean 128.20±4.49 mmol/L) and hypochloraemia (66 mmol/L to 108 mmol/L, mean 87.90±10.12 mmol/L). The causes of the electrolyte disturbances could have been the renal injuries and the low intake of food. The recovery of hypokalemia was very slow with 18 d as the longest period.

None of the children exhibited respiratory symptoms and abnormal arterial blood gas (ABG) analysis results within 24 h.The respiratory symptoms began about 5 d after poisoning (e.g., chest tightness) with pH (7.44±0.03), PaO2 (67.38±4.41 mmHg), PaCO2 (37.73±2.51 mmHg), HCO3−(25.22±2.10 mmol/L) and SaO2 (90.61±2.02 %). The abnormal ABG analysis results of eleven children with progressive dyspnea were due to respiratory alkalosis within 7 d to 10 d after poisoning with pH (7.54±0.06), PaO2 (48.42±3.67 mmHg),PaCO2 (29.16±2.90 mmHg), HCO3− (25.34±1.50 mmol/L)and SaO2 (81.14±3.39 %). The hyperventilation due to hypoxemia had resulted in decline PaCO2 levels and elevated pH values. Treatment through oxygen inhalation could not effectively ameliorate hypoxemia. The continued type I respiratory failure state did not improve in 14 d of exposure, with pH (7.49±0.04), PaO2 (37.56±5.08 mmHg), PaCO2 (32.76±2.81 mmHg), HCO3−(24.74±1.61 mmol/L) and SaO2 (71.78±6.08 %), which ultimately resulted in the death of the children. No apparent abnormal ABG analysis results of survivors were detected during their hospital stay. Lung injuries were found in five children through CT examination. The lung markings increased within 3 d to 5 d after poisoning. Pulmonary alveoli exudation and consolidation appeared within 7 d to 10 d after poisoning. Pulmonary fibrosis ultimately appeared on approximately the 14th day after poisoning. However, a 4-y-old child had lobus medius pulmonis fibrosis, 6 d after poisoning. The brain MRI examination of a 12-y-old boy with seizures after poisoning showed pallium abnormal signals. These abnormal phenomena signified toxic encephalopathy. The brain MRI was reviewed 7 d after the seizures and showed that the extent of lesion has decreased. All children were given gastric lavage, gastrointestinal mucoprotective agent, liver and myocardium protection, cell anti-oxidants and other treatments. All patients were initially administered glucocorticoid treatment. Methylprednisolone (20 mg/kg/d×3d) was given as an impulse treatment. Gamma globulin (2 g/kg divided into 3 d to 5 d) was simultaneously given. Prednisone was given orally for 4 wk to 8 wk. The oxygen inhalation and mechanical ventilation treatments were carefully chosen because these treatments could aggravate pulmonary fibrosis through the excessive production of oxygen free radicals. Children were given hemodialysis or

peritoneal dialysis if the creatinine (Cr) level was higher than 500 μmol/L.

Nine children died during hospitalization, one children abandoned therapy and four children exhibited improved conditions, which allowed them to be discharged from the hospital. Four children remained alive until April 2019.

The total mortality rate was 9/14(64.28%). The plasma paraquat levels of the surviving patients were obviously lower than the dead ones. The peak levels of ALT, AST, GGT, TBIL, DBIL, IBIL, BUN and Cr in the surviving patients were noticeably different from those of the dead ones. The highest levels of pH and the lowest levels of PaO2, PaCO2 and SaO2 were also different between the surviving and dead patients. The correlation analysis of the plasma paraquat level with the highest level of the pH and the lowest level of PaO2, PaCO2 and SaO2, revealed that the plasma paraquat level was positively related to the pH value (rho=0.550, P=0.008), and was negatively related to the level of PaO2 (rho=−0.627, P=0.002), PaCO2(rho=−0.552, P=0.008) and SaO2 (rho=−0.554, P=0.007).

Table-1: Clinical Manifestations of Patient with Paraquat Poisoning

Clinical manifestations	Number of patients (%)
Vomiting	14/14(100)
Alimentary tract hemorrhage	8/14(57.14)
Abdominal pain	8/14(57./.14)
Oppression in chest	11/14(78.5)
Dyspnea	8/14(57.14)
Fever	1/14(7.14)
Oliguria	7/14(50)
Microscopic hematuria	7/14(50)
Proteinuria	5/14(35.71)
Dizziness	4/14(28.57)
Seizure	1/14(7.14)

Table-2: Patient Characteristics

No of patients	14
Male : female	12:2
Mean age (years)	9±3
Amount of paraquat ingested <10 ml of concentrate 10-20ml of concentrate >20ml	No of patients 1 (7.14%) 5(35.71%) 8(57.14%)
Duration(hours) from ingestion to admission <6 hours 6-24 hrs >24hrs	No of patients 2(14.28%) 6(28.57%) 8(57.14%)

Table-3: Prognosis of poisoned cases

PROGNOSIS	No of patients
Recovery	4(28.57%)
LAMA(Left against medical advice	1(7.14%)
Mortality(total) Mortality (after 24hr.of ingestion)	9(64.28%) 3(33.33%)

DISCUSSION

Oral intake of paraquat was the most frequent route of poisoning. Paraquat is bipyridilium herbicide, which is inactivated by adsorption to clay in the soil 1. The toxicity of paraquat is through redox cycling, leading to generation of superoxide anions. These may react to form hydrogen peroxide and subsequently the highly reactive hydroxyl radical, which is thought to be responsible for lipid peroxidation and cell death. A second contributing factor to toxicity is the depletion of nicotinamide adenine dinucleotide phosphate with bound hydrogen ion (NADPH), as both paraquat redox cycling as well as hydrogen peroxide detoxification via glutathione is NADPH dependent 4.

The clinical course of the disease depends on the amount ingested. The plasma paraquat level reached the peak within 1 h to 4 h after poisoning, then decreased through renal excretion and tissue deposition, including lung, liver, kidney, body fluids and muscle. Paraquat can deposit in great amounts in the lung. The

lung tissue concentration could maintain a high level even with the decrease of the plasma concentration, which leads to long-lasting and persistent lung injury [1]. This phenomenon was obvious in the index study. Pulmonary fibrosis was the most common long-term complication of paraquat poisoning. The mechanism of paraquat toxicity was not completely clear. Paraquat toxicity is consistently viewed as having two aspects: oxygen-derived free radicals [2, 3] and mitochondrial injuries [4]. In the present study, the alimentary tract symptoms were extensive, which indicated powerful mucous membrane contact injury effect of paraquat. A12-y-old boy had serious seizures. Huang *et al.*, reported five cases with paraquat-induced convulsions and death [5]. Epilepsy-like convulsions induced by paraquat were believed to result in death despite being seldom observed. Wu *et al.*, found apparent microglia activation in substantia nigra and striatum within 1 wk after intoxication using the rat paraquat-poisoning model. Astrocyte edema and neuron apoptosis were also observed in the rat [6]. MRI was used to study the neuroimaging of patients with paraquat poisoning which revealed that paraquat could damage the CNS in acute phase and in recovery phase [7]. The CNS toxicity of paraquat frequently focuses on the substantia nigra. Paraquat could induce caspase-3 expression in substantia nigra neurons and hasten neuron apoptosis. However, Bartlett *et al*., reported that paraquat cannot pass through the blood brain barrier in rhesus macaque [8], thus the mechanism of CNS injury remains unclear to date. No specific antidotes for paraquat poisoning are available. The key point of the treatment is to control pulmonary fibrosis. Glucocorticoids and immunosuppressive agents are usually used to treat pulmonary fibrosis. Lin *et al*., reported the use of methylprednisolone (1 g/d×3d) and cyclophosphamide (15 mg/kg/d×2d) as pulse therapy in the beginning, followed by dexamethasone (20 mg/d) until PaO2>80 mmHg. The researchers used methylprednisolone (1 g/d×3d) and cyclophosphamide (15 mg/kg/d×1d) if PaO2<60 mmHg.

This protocol could obviously improve survival rate [9]. They also reported that repeated pulses of methylprednisolone and cyclophosphamide were better in reducing mortality rate than high doses of dexamethasone and cyclophosphamide [10]. However, we found that glucocorticoids did not have a good long-term effect. Tasi *et al*., showed that methylprednisolone pulse therapy did not effectively treat paraquat poisoning [11]. Zhi *et al*., also reported that Edaravone could effectively treat pulmonary injury induced by paraquat as a free radical scavenger [12]. Mohammadi-Karakani and Ghazi-Khansari *et al*., reported that captopril and lisinopril could ameliorate paraquat toxicity in the mitochondria [13, 14]. Glutathione reductase and pirfenidone reportedly ameliorate paraquat toxicity in the CNS and lungs [15, 16]. In the present study, We found that pulmonary fibrosis could not be reversed and that the prognosis of paraquat poisoning is still pessimistic even with the use of large dose of methylprednisolone and long-term oral prednisone. Tsai *et al*., reported that young age, low plasma paraquat level, low Cr level, female gender and low elapsed time since poisoning could predict high survival rate [11]. In this study, surviving patients were younger, and that their plasma paraquat levels were lower compared with the dead patients. The authors believed that younger children possibly came in contact with paraquat accidentally, whereas the older children possibly took oral paraquatde liberately, which accounted for the higher dose taken.The peak ALT, AST, GGT, TBIL, DBIL, IBIL, BUN and Cr levels of the surviving patients were noticeably different from those of the dead patients, but the authors found that these indices had improved before death. Yang *et al*., found that the spectrum of liver injury in patients with paraquat poisoning is mild and transient, which doesnot cause death [17]. Acute kidney injury is frequently reported with paraquat poisoning in humans [18]. In this study, we found that the spectrum of liver and renal injury was the common manifestation of paraquat poisoning in children, but the injury was transient and non-fatal. The spectrum of lung injury, which was developing and fatal, was different from that of the liver and renal injuries. Huang *et al*., reported the correlation between paraquat amount, plasma paraquat concentration, base excess value and survival time [19]. A positive relationship was found between the plasma paraquat level and pH value, and negative relationship was found between the plasma paraquat level and the level of PaO2, PaCO2 and SaO2. So plasma paraquat level may be a significant factor in the prognosis of paraquat poisoning in children. Arterial lactate and pentraxin-3 were also reported as prognosis predictors for paraquat poisoning [20, 21]. However, no recognized index was found that could accurately predict prognosis.

CONCLUSION

The children suffering from paraquat poisoning had multisystemic injuries. Progressive respiratory failure caused by pulmonary fibrosis, was the primary cause of death. The treatment was difficult. Methylprednisolone and Gamma globulin therapy took effect in the early stage, but the long-term prognosis remained pessimistic. No recognized indicator that could accurately predict prognosis. However,the plasma paraquat level may be a potential predictor.

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