

Paraquat poisoning in Andaman and Nicobar Islands – Government must intervene

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ABSTRACT

Paraquat poisoning is a grave public health problem in the Andaman and Nicobar islands of India. To evaluate various aspects of paraquat poisoning that influence the outcome, a retrospective study was planned. In this case series study, the information about all cases of acute paraquat poisoning who were admitted to GB Pant Hospital, Port-Blair, in a 12-year period (January 2007–December 2018) were evaluated. A total of 29 referred patients were evaluated with the majority from the early productive age of 16–30 years (68.97%). The case fatality rate was 100%. Most of the incidents took place in South Andaman district (68.97%) and during the rainy season (55.17%). Initially, they presented with local symptoms like mouth and throat pain with ulceration (48.27%), vomiting (44.82%), breathlessness (34.48%), epigastric and abdominal pain (31.03%), hematemesis (27.58%), and oliguria (20.68%). Later on, major organ dysfunctions like a respiratory failure (65.51%), acute kidney injury (62.08%), acute liver failure (55.17%), cardiac dysfunction (31.03%), and multiorgan failure (58.62%) ensued. Patients who were referred early had a significantly longer hospital stay. Few received advanced care, like, methyl prednisolone (24.12%), cyclophosphamide (10.34%), Mesna/NAC (06.89%), charcoal tablets (10.34%), mechanical ventilation (06.89%), and hemodialysis (10.34%). Apart from hemodialysis in acute kidney injury patients and steroid pulse, no other modalities showed improved hospital survival duration. Primary prevention especially government laws, public awareness, and education of health professionals regarding the seriousness of this problem are the keys to get rid of this incurable poisoning in these islands. The government should prioritize preventive works in the south Andaman district and during the rainy season to avoid catastrophe each year and if possible should ban it. Methyl prednisolone therapy and hemodialysis might be advocated to have a better outcome.

Keywords: Ban, immunosuppressive therapy, paraquat poisoning, reactive oxygen species, survival

Introduction

Paraquat (1, 1'-dimethyl-4, 4'-bipyridiniumdichloride) poisoning is a grave public health problem especially in developing countries.^[1] This broad-spectrum herbicide is commercially available as a brownish concentrated liquid under the trade name of 'Gramoxone' for agricultural use and as brown granules of

'Weedol®' for horticultural use. Exact prevalence of paraquat poisoning in India is not known due to non-reporting, diagnostic dilemma, and limited case reports or case series mainly from North India.^[2] Ingestion is the most common route of poisoning. After ingestion it is quickly absorbed from the gut and within first 6 hours, 95% of absorbed poison is distributed in body tissue with a chance of late redistribution in plasma. It is excreted mainly through the kidneys within first 12-24 hours.^[3] A dose of about 30 mg/kg or 20 mL of 20% solution can be fatal to adults.^[3,4] The major mechanism of poison-related organ dysfunction is the generation of reactive oxygen species causing

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damage at the intracellular level resulting in lipid peroxidation of cell membrane, destruction of the cell membrane structure, mitochondrial toxicity, oxidation of NADPH and NF-kappa B, and apoptosis.^[5,6]

Along with severe irritative and ulcerative local symptoms lungs, heart, kidneys, liver, adrenals, central nervous system, muscles, and spleen are the major organs affected in the toxicity.^[7] Due to these end-organ damages and lack of a definitive treatment (no available guideline) the mortality is 40-50% in most cases, approaching to almost 100% in cases with intentional self-poisoning with concentrated formulations.^[7] Indian patients have higher mortality in the range of 50-100% based on a few case series published^[8] The cause of this is not known exactly but mostly relates to late referral to hospital, high amount of ingestion, and less use of immunosuppressive agents for treatment.^[9,10] Data analysis of medical record section is showing that an average of two to five cases of the poisoning per year are getting admitted with 100% mortality in GB Pant hospital, the only tertiary care center, in Andaman and Nicobar Islands of India.

The primary objective of this retrospective case series study is to analyze the demography, clinical symptoms and signs, laboratory abnormalities, and treatments of the paraquat poisoning admitted here over the last 12 years period. Secondly, we have tried to establish the cause of early or late death through regression analysis.

Case Series

The study was done in GB Pant hospital (recently upgraded to a medical college), Port Blair (capital of Andaman and Nicobar, a union territory of India). This territory had 572 islands out of which 325 in the Andaman and 247 in the Nicobar. The population of Andaman and Nicobar islands in early 2019 as per estimate was 434,024. Total available health care facilities in this territory were tertiary care center (1), secondary care center (8), primary care center (22), urban health center (5), sub-center (114), homeopathy dispensary (8), and ayurvedic dispensary (1).^[11]

This was a retrospective case series study of all the patients admitted to the GB Pant hospital with alleged paraquat poisoning (medico-legal case category) in last the 12 years (2007–2018). Data was obtained after retrieving patients' file from the medical record section of the hospital with prior approval from the hospital superintendent as there was no existent institutional review board or ethical committee. All the data were kept strictly confidential.

Hospital medical records from January 2007 to December 2018 revealed that there were 29 admitted patients of alleged paraquat poisoning. Demographic details were described in Table 1. All patients were referred from local health centers; mostly they were located in south Andaman district [Figure 1]. Maximum number of cases (50%) were from two PHCs, named RK Pur and Manglutan. Prevalence was almost equally distributed among

male and female population. Majority were from early productive age group, that is, 16–30 years. During the rainy season most of the cases were encountered. Most of the cases were without any known comorbidities or any addictions.

Due to non-availability ICU beds most of the patients were treated in general medical ward [Table 2]. The only mode of poisoning was found to be oral ingestion. The known amount of poison killing all patients were as low as 20 mL to as high as 200 mL. Average duration (hours) of survival was 5 days. Mortality was categorized into early (≤ 5 days) and late (> 5 days). They mostly presented with local oral and throat complaints before organ failure. Examination at the time of admission confirmed the same. Later on during hospital course features of multiple organ involvement were evident. Lungs, kidney, and liver, respectively, were involved in more than 50% patients. And more than half of the patients ultimately developed features of multiorgan failure (≥ 2 organs) leading to death. However, sepsis was rare. Cardio-respiratory failure or cardiac arrest were wrongly stated as terminal event. Modalities of treatment offered to them were gastric lavage with or without activated charcoal, IV Fluid, antibiotics, proton pump inhibitors, anti-emetics, and Mesna with other supportive care [Table 2]. Immunosuppressive therapy was tried in seven patients in the form of Inj methyl prednisolone 1 gm IV 24 hourly for three days and Inj cyclophosphamide 750 mg/dose for three doses. Hemodialysis was done in three patients with acute kidney injury.

All cases died after a variable period of hospital stay (100% mortality). Comparative analysis of early (≤ 5 days) and late (> 5 days) deaths was done with the help of Chi-square test [Table 3].

Table 1: Demographic characteristics of the patients of paraquat poisoning (n=29, % in bracket)

Categories	Frequency
Sex	
M	14 (48.28)
Age	
01-15 years	01 (03.4)
16-30 years	20 (68.97)
31-45 years	07 (24.13)
46-60 years	01 (03.4)
>60 years	00
Residence (district wise)	
North and Middle Andaman	07 (20.68)
South Andaman	20 (68.96)
Little Andaman	01 (03.4)
Nicobar	01 (03.4)
Early Referral (<24 h)	15 (51.72)
Season during admission	
Summer (January-March)	10 (34.48)
Rainy (April-September)	16 (55.17)
Spring (October-December)	03 (10.34)
Known comorbidities	
RHD, post PTMC	01 (03.44)
Epilepsy	01 (03.44)
Alcohol dependency	01 (03.44)
HAP With <i>Staph aureus</i>	01 (03.44)
Ingested with alcohol	04 (13.79)

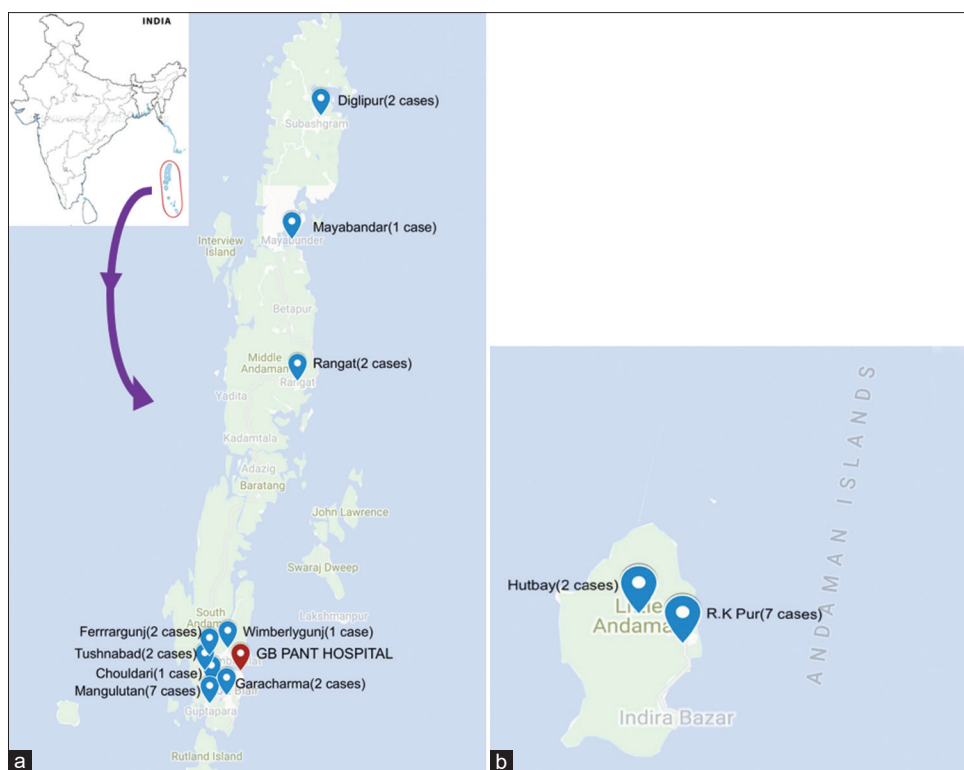


Figure 1: Map of India (inlet) with Andaman and Nicobar Islands. Primary health care wise distribution of paraquat poisoning patients who have been referred to our hospital (GB Pant hospital) from many north, middle, and south Andaman islands (a) and little Andaman (b). Map courtesy: Terrain map scaled down from Google Map[®] – modified in compliance with in-app permissions and policies

Discussion

Paraquat intoxication poses a major public health problem as it is easily available and lethal in adequate doses. Till date there is no specific antidote to paraquat. Only supportive and symptomatic management are offered. In this study we describe the clinico-demographic pattern of the poisoning along with causal relationship of various factors pertaining to mortality and focus on possible solutions in medically underprivileged areas of Andaman and Nicobar islands. Unfortunately, none survived in our study.

Significant seasonal variation of paraquat poisoning is observed in Amiri *et al.*^[12] study who reports more prevalence in the summer and in spring and summer in Delirrad M *et al.* study. However, our study shows >50% cases appear in rainy season followed by in summer. This may be due to climate of the islands, that is, tropical where rainfall occurs for the majority of the year from April to September along with other two prevalent seasons summer (January to March) and spring (October to December).^[13] Paddy, coconut, and areca nut are the main crops of these islands and reared in rainy season and paraquat is easily available for agricultural use. Furthermore, the connectivity to our hospital is by roads, water, and/or air. Transportation is particularly hazardous during the rainy season possibly causing further worsening of health facilities. Causes of delayed referral are mostly related to poor transport facilities or diagnostic problems and this is one of the major reasons for early death.

The paraquat poisoning in most of the studies is more common in men (55-70%), most likely due to more involvement in agricultural activities and easy access.^[3,4,14] However in our study no gender preponderance is found. Majority of patients belong to early productive age group, that is, 16–30 years similar to other studies.^[3,14] Intentional exposure with suicidal attempt is reported to be the most common cause of intoxication in most studies similar to our study.^[12,15] In most of the studies the lethal dose of the poison is proposed to be >20 mL and substantial chances of recovery are inversely proportional to amount ingested.^[14] In our study exact amount of ingestion could be determined in only 37.93% of patients and each dose proved to be fatal with the lowest being 20 mL. As it is 100% fatal in these islands with limited medical services, government should ban similar to >60 countries who have banned this fatal herbicide. If availability is there then apart from these noticeable two to three deaths per year, many preventable deaths will continue. In one recent study in Taiwan, it was expected to reduce 200 deaths per year after banning the said poison.^[16]

Paraquat ingestion is associated with noticeable local effects as evident with higher frequencies of oral ulceration and epigastric pain before systemic effects set in.^[14,17] However, another study has reported that all patients diagnosed with the poisoning experienced nausea and vomiting, but oral mucosal ulcers are reported in only 59% cases.^[18] Our study agrees with former studies with evidence of oral ulceration in majority of patients.

Almost every major organs are affected in the poisoning with lungs being most common and central nervous system least common.^[3,14] Patients with even single major organ involvement are associated with early mortality. Sequential organ failure leading to death is observed in most of the cases. In fact, consuming higher doses of poison can lead to death during the first few hours through acute multi-organ failure.^[19] Pulmonary fibrosis is among the known complications in paraquat poisoning which occurs approximately 7 to 14 days after the poisoning along with acute respiratory failure.^[20,21] In our study patients did not survive enough to develop pulmonary fibrosis and also no measures were taken to assess degree of fibrosis.

Recently role of antioxidants, like, *N*-acetyl cysteine, vitamin E and C, and immunosuppressive therapy, like, pulse steroids and cyclophosphamide are being evaluated in various specialized centers with variable results.^[10] In our study, treatment with charcoal, Mesna, even immunosuppressive therapy could not alter the course of the disease significantly. However, methyl prednisolone pulse therapy has some response with longer hospital stay ($P = 0.06$). Delirrad M *et al.*^[3] shows neutral effect of hemodialysis on patient's outcome. However in our study hemodialysis in patients with renal failure is associated with improved outcome in terms of hospital survival duration, whereas mechanical ventilation failed to do so in patients with respiratory involvement. As there are many studies showing survival of patients treated with anti-oxidants, immunosuppressive therapy, timely hemodialysis along with other supportive management. With 100% case fatality in our study it seems time is the most important factor. Results from our study indicate that majority mortality occurs on or before the fifth day of hospitalization similar to other studies.^[14,22] Early referral to specialized center is associated significantly with higher in hospital survival duration. Early implementation of anti-oxidants and immunosuppressive therapy with aggressive organ supportive therapy could have altered the disease course because once the damage reaches the stage of irreversibility even with best possible management death is inevitable.

Limited data exists regarding amount of toxin ingested and mode of ingestion whether intentional or accidental. Serum and urinary level of paraquat were not determined. Serial monitoring of all laboratory parameters is not done including chest imaging to assess the pulmonary fibrosis. Specialized care, that is, hemodialysis, mechanical ventilation, and immunosuppressive therapy are tried in relatively less number of patients.

Conclusion

Extremely lethal paraquat poisoning is a major public health concern in Indian islands with documented 29 deaths in 12 years of average 434,024 populations (2019 census). Being incurable in these islands, primary prevention and early aggressive management are the keys to get rid of this problem. Public awareness and education of health professionals regarding seriousness of this problem and early identification of signs and symptoms of intoxication are essential. Government should be more proactive regarding early referral of

Table 2: Clinical profiles of all patients of paraquat poisoning (n=29, % in bracket)

Categories	Frequency
Admission	
Ward	22 (75.86)
ICU	07 (24.13)
Amount ingested	
Known amount (mL)	11
Max	200
Min	20
Mean	77
Survival times (h)	
Max	390
Min	5
Mean	106.26
Presenting complaints	
Mouth and throat pain with ulcer	14 (48.27)
Vomiting	13 (44.82)
Shortness of breath	10 (34.48)
Epigastric and abdominal pain	09 (31.03)
Hematemesis	08 (27.58)
Oliguria	06 (20.68)
Dysphagia	05 (17.24)
Chest pain	04 (13.79)
Dysphonia	04 (13.79)
Loose stool	04 (13.79)
Hematuria	04 (13.79)
Fever	03 (10.34)
Burning body	03 (10.34)
Seizure	02 (6.89)
Hemoptysis	02 (6.89)
Malena	01 (3.44)
Jaundice	01 (3.44)
On examination	
Oral ulceration	18 (62.06)
Epigastric tenderness	08 (27.58)
Icterus	07 (24.13)
Crackles	04 (13.79)
Organs involvement (laboratory wise)	
Lungs	19 (65.51)
Kidney	18 (62.06)
Liver	16 (55.17)
Cardiac	09 (31.03)
Pancreas	06 (20.68)
Multi-organ failure (MOF)	17 (58.62)
Terminal events before death	
MOF	17 (58.62)
Cardiac arrest	09 (31.03)
Cardio-respiratory arrest	03 (10.34)
Pancreatitis	01 (3.44)
Acute kidney injury	01 (3.44)
Sepsis	01 (3.44)
Treatment characteristics	
Gastric lavage	20 (68.97)
Administration of activated charcoal	03 (10.34)
Insertion of nasogastric tube	29 (100.0)
Use of methyl prednisolone -	
Complete dose	06 (20.68)
Incomplete dose	01 (03.44)
Use of cyclophosphamide -	
Complete dose	02 (06.89)
Incomplete dose	01 (03.44)
Use of Mesna/NAC	02 (06.89)
Mechanical ventilation	02 (06.89)
Hemodialysis	03 (10.34)

Table 3: Various parameters in relation to late death (>5 days hospital stay)

Parameters	P
Sex (M)	0.0689
Referral status (early)	0.0
ICU admission	0.137
AKI (absent)	0.001
Acute liver injury (absent)	0.0
Respiratory failure (absent)	0.003
Multiorgan failure (absent)	0.0
Gastric lavage	0.09
Charcoal use	0.174
Mesna use	0.111
Use of methyl prednisolone pulse	0.06
Use of cyclophosphamide pulse	0.159
Hemodialysis in renal failure patients	0.029
Mechanical ventilation in respiratory failure	0.846

the affected victims to nearby specialized centers. Organ supportive therapy is crucial including hemodialysis. Best possible curative therapy based on recent evidence should be started at the earliest especially pulse methyl prednisolone. Role of immunosuppressive therapy should be ascertained with further clinical trials including specific guideline for the management. Moreover, Indian government should focus on proper implementation of the Indian Insecticides Act to reduce indiscriminate use or ban and stop widespread availability of this deadly poison.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined not to require Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is not applicable as this was a retrospective case series study.

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Conflicts of interest

There are no conflicts of interest.

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