ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY
APJMT 14;4 http://apjmt.mums.ac.ir December 2025

SHORT COMMUNICATION

A Promising New Therapeutic Strategy to Improve Mortality Outcomes in Patients with Moderate to Severe Paraquat Poisoning

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Abstract

***Background*:** Paraquat ingestion is associated with multi-organ failure and high mortality. The lack of management guidelines and an appropriate antidote is concerning. This report discusses the successful treatment and management of four patients at our tertiary hospital using a novel combination protocol.
***Methods*:** We treated four patients with paraquat ingestion who presented to our center with a novel combination protocol, which included administration of intravenous Methylprednisolone, N-acetylcysteine, Cyclophosphamide, oral Vitamin C and Vitamin E, and an antifibrotic agent. We followed up with these patients in the hospital, monitoring their clinical outcome.
***Results*:** The ingested volume of paraquat ranged from 10 ml to 50 ml of 24% paraquat. Three patients had paraquat tongue with corrosive injury. We noted a serial rise in creatinine levels in all patients, which returned to baseline on follow-up. Three patients had ground-glass opacifications on a high-resolution Chest computerized tomography scan. At follow-up, we noted normal renal and liver function, with no delayed effects or complications in these patients.
***Conclusion*:** A combination therapy with immunosuppression, high-dose antioxidants, and antifibrotics has demonstrated potential in treating paraquat (PQ) poisoning, preventing progressive pulmonary fibrosis, and improving survival. This protocol has shown progress in PQ poisoning management and has laid the groundwork for future research.

Keywords: Paraquat, Multiple Organ Failure, Pulmonary fibrosis, Immunosuppression Therapy, Antioxidants

How to cite this article: Philip B, Jayakaran JAJ, Newbigging NS, Pichamuthu1 K, Iyadurai R. A Promising New Therapeutic Strategy to Improve Mortality Outcomes in Patients with Moderate to Severe Paraquat Poisoning. Asia Pac J Med Toxicol 2025; 14(4): 173-7.

INTRODUCTION

Deliberate self-harm using pesticides is a significant public health problem prevalent in most developing countries, with an estimated 300,000 deaths per year occurring in the Asia–Pacific region [1]. Paraquat (1,1′-Dimethyl-4,4′-bipyridinium dichloride), a commonly used chemical herbicide for clearing weeds in India [2, 3], is a contact poison and desiccant [4, 5]. The World Health Organisation categorizes Paraquat (PQ) as a Class II moderately hazardous pesticide. Humans can get exposed to PQ either by accidental contact with the skin, eyes, etc., or intentional ingestion as a measure of suicide. Deliberate self-harm with PQ is a cause of significant morbidity and mortality due to the lack of a specific antidote [6]. While the organophosphate class accounts for the majority of hospital admissions, the exceptionally high case fatality (> 50%) of PQ means that it is the single leading agent causing death owing to chemical poisoning in many countries [1]. The lethality of the compound has been widely discussed worldwide. Hence, it is banned in many countries in Europe and also in South Asian countries like Sri Lanka [1] and Malaysia [7], while India does not have stringent laws to prevent PQ use and misuse.

PQ generates highly reactive oxygen species (ROS), which damage the lipid membrane of cells through peroxidation, inducing cellular toxicity in organs, especially the pulmonary alveolar epithelium [6, 8] as PQ is taken up against a concentration gradient in the lung. PQ causes an acute inflammatory response, resulting in renal failure, toxic hepatitis, cardiac failure, hypotension, convulsions, eventually leading to pulmonary fibrosis, and ultimately, death [3]. At high doses, PQ is known to cause rapid deterioration and death due to multi-organ failure [9]. Even at moderate doses, it can cause progressive delayed pulmonary fibrosis between 2-4 weeks from ingestion [9].

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Hence, halting the inflammatory response can prevent multi-organ failure, pulmonary fibrosis, and death. The very high case fatality rate of PQ poisoning is due to the lack of any effective treatment. There are no accepted guidelines for the treatment of patients with PQ poisoning [1].

Treatment varies from supportive care alone to a combination of immunomodulation, antioxidants, hemoperfusion, and hemodialysis [1, 6]. Several treatments have been investigated to attenuate the profound ROS-driven inflammatory response, including pulse therapy [10] and prolonged immunosuppression therapy with cyclophosphamide and methylprednisolone [11], administered independently or in combination [1, 4,11–13]. Additionally, studies have investigated the use of antioxidants, such as N-acetylcysteine, Vitamin C, Vitamin E, and Glutathione, as well as antifibrotic agents like Pirfenidone [14–18]. N-acetylcysteine (NAC), high doses of Vitamin C, and antioxidants have shown some promise in reducing mortality in PQ poisoning cases. NAC replenishes cysteine and increases glutathione levels, thereby reducing PQ-induced apoptosis and inflammatory markers [1, 14, 19, 20]. Vitamin C can neutralize free radicals and Vitamin E has shown some reduction in lung toxicity in animal models [16, 18, 21, 22]. Antifibrotics, such as Pirfenidone and Nintedanib, which are mainstay treatments for delaying fibrosis in Idiopathic pulmonary fibrosis, have also been studied for their effectiveness in halting fibrosis in PQ poisoning [17, 23, 24]. In our extensive literature search, we noted a lack of research or evidence on treatment with a combination of immunosuppression with cyclophosphamide and steroids, high-dose antioxidants, and antifibrotics. The objective of this study is to report the effectiveness of a combination treatment protocol with immunosuppression, high-dose antioxidants, and antifibrotics, aimed at the toxicodynamics of PQ, through a case series of successfully treated patients.

METHODS

We treated four patients with PQ poisoning with a combination protocol from Day 1 of admission which included:

1. Extended pulse administration of Intravenous Methylprednisolone at a dosage of 15mg/kg/day for six days, followed by intravenous/oral Methylprednisolone at progressively halved doses every 2 days until reaching 0.47mg/kg/day.
2. Intravenous Cyclophosphamide 15 mg/kg for two days [between day one and day 7 of admission].
3. Intravenous NAC infusion at 150 mg/kg in 200 mL of 5% Dextrose over 15-60 minutes, followed by 50 mg/kg in 500 mL of 5% Dextrose over 4 hours, and subsequent doses over 8 hours, followed by oral NAC 600 mg thrice daily from day 1 of admission till day 30.
4. High-dose Vitamin C and Vitamin E from day 1 of admission till day 30.
5. Antifibrotic, either Pirfenidone or Nintedanib, from day 1 of admission till day 30.
6. Supportive management like intravenous hydration, early endoscopy guided nasogastric tube placement and feeding, proton pump inhibitors, oral anaesthetic gel, and antacid syrups

We documented the clinical and laboratory parameters and performed high-resolution computed tomography [HRCT] of the thorax at intervals to determine the extent of PQ-related lung injury. We followed up with these patients at 30 days as outpatients and 6 months via telephone.

RESULTS

Patient 1

A 35-year-old male presented with recurrent vomiting and one episode of hematemesis, 9 hours after ingesting 10 ml of 24% PQ. Creatinine concentration showed an initial increase, normalized by day 19 of treatment, with the highest concentration of 4.98 mg% (Figure 1). He did not require oxygen supplementation throughout the treatment period. HRCT-Thorax done on day 9 showed no findings suggestive of PQ-related lung injury. At the 6-month follow-up, he was alive without any symptoms.

Patient 2

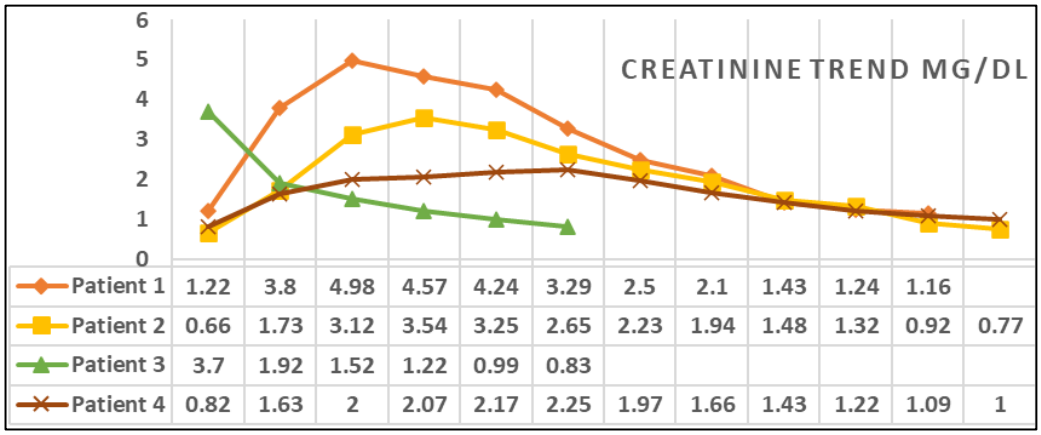
A 27-year-old male presented with two episodes of vomiting, 14 hours following the ingestion of 50 ml of 24% PQ. Creatinine concentration increased initially, which returned to baseline by day 24 of treatment, with the highest concentration of 3.54 mg% (Figure 1). The patient did not require oxygen supplementation throughout the treatment period. HRCT-Thorax done on day 7 revealed post-inflammatory linear atelectatic bands in a lung segment, and subsequent HRCT-Thorax on day 24 showed sub-pleural band-like opacities with ground glass densities in bilateral lower lobes with traction bronchiectasis. He developed Serratia species bacteraemia during admission and was treated as per antimicrobial sensitivity for 14 days. At the 6-month follow-up, he was alive without any symptoms.

Patient 3

A 22-year-old male presented with throat discomfort and difficulty swallowing liquids and solids 12 days after ingesting 10 ml of 24% PQ. At admission, his creatinine concentration was 3.70 mg/dl, and returned to baseline by day 12 of treatment (Figure 1). The patient did not require oxygen supplementation throughout the treatment period. On day 14 of ingestion (day 3 of treatment), an HRCT-Thorax showed faint patchy ground-glass densities in multiple segments of bilateral lungs. A subsequent HRCT-Thorax on day 25 of ingestion (day 14 of treatment) revealed small band-like subpleural densities in multiple segments, with traction bronchiectasis and focal areas of ground-glass densities. At 6 months of telephonic follow-up, he was alive without any symptoms.

Patient 4

A 35-year-old female presented with episodes of vomiting, 7 hours following ingestion of 50 ml of 24% PQ. Her creatinine concentration showed an increasing trend, which returned to baseline by day 24, with a peak



Patient 1	1.22	3.8	4.98	4.57	4.24	3.29	2.5	2.1	1.43	1.24	1.16	
Patient 2	0.66	1.73	3.12	3.54	3.25	2.65	2.23	1.94	1.48	1.32	0.92	0.77
Patient 3	3.7	1.92	1.52	1.22	0.99	0.83						
Patient 4	0.82	1.63	2	2.07	2.17	2.25	1.97	1.66	1.43	1.22	1.09	1

Figure 1. The trend of creatinine (mg/dl) in four patients

concentration of 2.25 mg% (Figure 1). She had transaminitis on day 4, with peak Aspartate transaminase (AST) concentration of 232 U/L and Alanine transaminase (ALT) concentration of 316 U/L, which resolved by day 14. The patient did not require oxygen supplementation throughout the treatment period. An HRCT-Thorax on day 6 revealed scattered peripheral ground-glass densities in the bilateral lungs. HRCT-Thorax on day 29 showed an increase in the size of the densities along with traction bronchiectasis. At the 6-month telephonic follow-up, she was alive without any symptoms.

DISCUSSION

In our case series, all four patients had consumed PQ at a concentration of 24%, quantities ranging from 10 to 50 ml corresponding with moderate to severe toxic doses [6]. They were admitted within a period ranging from 9 hours to 11 days post-ingestion. All patients experienced vomiting and throat pain. Three out of four patients had paraquat tongue. In all patients, examination of the respiratory system was unremarkable, and they had optimal oxygen saturation in room air at the time of admission. At admission, all patients underwent upper gastrointestinal endoscopy for grading of corrosive injury and endoscopy-guided nasogastric tube placement to avoid blind insertion and risk of oesophageal perforation and pneumomediastinum. The patients were kept nil per oral for at least 24 hours from ingestion, following which they were started on oral feeds if tolerated or nasogastric tube feeds. They were immediately initiated on the combination protocol from day 1 of admission, which included high-dose intravenous methylprednisolone pulse for 6 days followed by tapering therapy, intravenous NAC infusion as per protocol, high-dose vitamin C and Vitamin E, along with an antifibrotic agent such as pirfenidone or nintedanib. They were also given two doses of intravenous cyclophosphamide pulses, administered over 2 days, between days 1 and 7.

On admission, renal function tests revealed elevated creatinine in one patient, while during the course of admission, all patients developed acute kidney injury. Serial monitoring of liver enzymes showed toxic hepatitis in one patient. HRCT-Thorax scans, taken after one week of ingestion, showed a normal study in one patient and PQ-related lung injury in the form of scattered ground-glass opacities in other patients, without any evidence of fibrosis. All patients received supportive treatment, including nasogastric feeds if oral feeds were not tolerated early endoscopy guided nasogastric tube placement, high-dose proton pump inhibitors, application of anaesthetic gel for paraquat tongue, antacid and sucralfate suspensions, and as-needed intravenous fluids. One patient developed Serratia species bacteraemia during admission and was treated as per antimicrobial sensitivity for 14 days. All four patients did not require oxygen supplementation throughout admission. All four (100%) patients had survived at the end of the hospital stay and were discharged after completion of the tapering course of prolonged intravenous methyl prednisolone. All patients were continued on NAC, Vitamin C, Vitamin E, and antifibrotic agents until 30 days post-ingestion.

The patients were followed up in the outpatient department at 1-week post-discharge and later at 1-month post-ingestion. All four patients demonstrated normal renal function and liver function test results at the 1-month review. One out of four patients showed mild interval progression of lung damage without fibrosis on serial CT imaging but reported no respiratory symptoms, exertional dyspnoea, or decreased effort tolerance. All patients were followed via telephonic interview for any symptoms of dyspnoea, cough, and decreased effort tolerance. All patients were alive without any disabling symptoms at 6-month telephonic follow-up.

All patients in our study, consuming moderate to severe amounts (> 10 ml), had AKI, while one patient had hepatitis.

HRCT-Thorax was normal in one patient, while three had PQ-induced lung injury without fibrosis. All four patients survived the moderate to severe PQ poisoning and demonstrated no progressive fibrosis on repeat HRCT-Thorax, done after 4 weeks from ingestion. In comparison, a retrospective analysis of 55 patients from a tertiary care centre in Southern India by Ravichandran et al [6] which reported moderate amount of PQ consumption in 54.5%, AKI in 81.8% hepatitis in 33.3% and use of steroids and cyclophosphamide alone as a combination in 30.9%, showed a mortality of 72.7% during hospital stay, with at least three more dying due to delayed pulmonary fibrosis after discharge [6]. Other studies also report high mortality rates, as follows: 61.4% by Rao et al., [25], 58.2% by Sandhu et al., [26], and 52% by Elenga et al., [27].

The study by Gao et al in China [11] demonstrated the potential of pulse methylprednisolone followed by prolonged tapering therapy, with a reported mortality of 47.4% compared to 63.3% in the pulse methylprednisolone-only group. The systematic review by Li et al., concluded that glucocorticoids, in combination with cyclophosphamide, in addition to standard care, were associated with a lower risk of death (RR 0.72; 95% CI 0.59-0.89) compared to standard care alone, affirming the effectiveness of the steroid-cyclophosphamide combination [12]. Hu et al., studied the role of a high-dose Vitamin C combination with steroids, showing a significant mortality difference (26.1% vs 100%) compared to steroids with low-dose Vitamin C and hemoperfusion therapy [28]. N-acetylcysteine and Vitamin E have not been extensively studied in human PQ poisoning cases, but they have shown great promise in animal models and few case reports [14, 16, 18–22, 29]. Pirfenidone has shown promise in recent studies in improving treatment efficacy in patients with pulmonary fibrosis [17] while Nintedanib hasn't been studied in paraquat poisoning. There are two distinct management philosophies in PQ poisoning: the first advocates for minimal low-risk interventions to keep patients comfortable. In contrast, the second firmly believes that no treatments are likely to be worse than the disease [1]. In the second context, a combination of all therapies was attempted in our patients, resulting in successful treatment of all patients characterized by improved survival (100%) and the prevention of progressive, delayed fibrosis.

The limitations of the study: This was a retrospective study with a small sample size of patients. Serum/Blood levels of Paraquat were not done in these patients due to non-availability of testing at our facility. Patients were not subjected to pulmonary function testing to ascertain functional status.

CONCLUSION

A combination therapy management approach has demonstrated potential in treating PQ poisoning, preventing progressive pulmonary fibrosis, and improving survival. This protocol has shown progress in PQ poisoning management and has laid the groundwork for future research.

ACKNOWLEDGMENTS

Not applicable.

Ethical approval: The project was reviewed and approved by the Institutional Review Board at Christian Medical College and Hospital, Vellore, India. IRB Min No. 2507134 [RETRO] dated 23.07.2025.

Declaration: We have not used any AI tools or technologies to prepare this manuscript.

Conflict of Interest: The authors report no conflict of interest to declare.

Funding and Support: None.

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