

# Management of Paraquat Poisoning—The Way Forward

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Paraquat (1, dimethyl-4-4bipyridylum dichloride-1) is a widely used herbicide owing to its low cost, availability, and good weeding activity. Ever since its use in 1958, deaths have been reported in developing countries following its consumption accidentally or with suicidal intent. Due to its highly toxic nature, its use has been labeled as restricted in many countries.<sup>1</sup> Paraquat has been banned in the European Union and Sri Lanka, being a menace to public health.<sup>2</sup> The first reported case of paraquat poisoning in India was in 1999,<sup>3</sup> and acute paraquat poisoning, which was an uncommon entity two decades ago, has turned into a common entity now.

Self-ingestion or cutaneous/mucosal contact can rapidly lead to multiorgan failure involving the respiratory, liver, and renal systems. Mild poisoning (based on the dose ingested) can present with gastrointestinal symptoms. In contrast, severe poisoning can lead to acute kidney failure, acute lung injury, and lung fibrosis resulting in death over 2–3 weeks. However, patients with fulminant poisoning (more than 40 mg per kg body weight) can develop complications within hours and die in 2–3 days.<sup>4</sup>

Paraquat exerts its toxic and lethal effects by forming cation radicals post-metabolism, subsequently generating free oxygen radicals, leading to mitochondrial damage and apoptosis. Lungs are affected the most as the chemical is sequestered here due to the concentration gradient, and alveolitis, alveolar damage, and fibrosis set in. Kidney failure occurs due to necrosis in the proximal convoluted tubule whereas acute liver injury occurs due to damage to the smooth endoplasmic reticulum and mitochondria, the distribution being high in these two organs. Gastrointestinal toxicity occurs in the form of mucosal lesions which can ulcerate and bleed, sometimes resulting in perforation of the tract and associated mediastinitis and pneumomediastinum.

In the absence of an antidote, and with a fatality rate as high as 90%, which can occur even with low doses, it continues to be a potential hazard and challenge for clinicians. There is currently no antidote with specific effects, for acute paraquat poisoning.<sup>5</sup> Measures for treatment include reducing poison absorption and eliminating absorbed poison, use of antioxidants, anti-inflammatory agents, and immunosuppressants, hemodialysis, and hemoperfusion, along with other supportive care.<sup>6</sup> These modalities though, are not based on guidelines or recommendations, and the supporting evidence is also weak, as it has been extrapolated from animal studies and case series in resource-limited settings, which lack information on the severity of the disease. The lack of definitive treatment can be attributed to the high fatality, apart from the inherent toxicity and its effects.

Though 90% of the compound is excreted in the urine unchanged within 12–24 hours post-exposure, it is the absorbed

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chemical that manifests the complications, and treatment interventions are aimed at it. Various studies have discussed the different treatment modalities and outcomes; however, data has been conflicting. It includes using methylprednisolone, dexamethasone, vitamin C, vitamin E, N-acetyl cysteine, and cyclophosphamide. Renal replacement therapy (intermittent or continuous) has shown survival benefits and hemoperfusion (repeated or continuous) has also been recommended to maintain a plasma level of <0.1 mg/L in view of a large volume of distribution and slow intercompartmental transfer,<sup>7</sup> and it needs to be performed at the earliest.

In 2007, Agarwal et al. did a retrospective analysis of 5 patients with paraquat poisoning in India; until then, only one case had been reported in the literature taking the tally to a total of 6 cases at that point of time. Immunosuppressive treatment was given to all patients while hemodialysis was done for patients with renal failure; 2 out of the 5 patients survived in their study.<sup>8</sup> In a systematic search of human studies, Gawarammana and Buckley in 2011 found that the case fatality was high despite the use of hemodialysis or hemoperfusion. They suggested that the efficacy of immunosuppression and antioxidants was anecdotal.<sup>9</sup>

However, another three randomized controlled trials compared dexamethasone, methylprednisolone, and cyclophosphamide with standard treatment, and all three showed mortality benefit in the treatment arm compared to the standard treatment.<sup>10</sup> Studies on human subjects have shown that high doses of vitamin C reduced mortality in a case series of 10 patients.<sup>11</sup>

A systematic review and meta-analysis in Iran in 2022, studied 44 patients where all required mechanical ventilation, and despite hemodialysis, there was no reduction in mortality. The reason cited was delayed presentation beyond 6 hours in most cases.<sup>12</sup>

Rao et al. had studied 101 patients of paraquat poisoning in the past and reported a 61.4% mortality. 63 patients received hemoperfusion, and mortality was seen in 42.9% of these patients, while mortality was 92.1% in patients who did not receive hemoperfusion. They emphasized the use of hemoperfusion within 6 hours for improved outcome.<sup>13</sup>

Different combinations of hemoperfusion and continuous renal replacement therapy are currently being performed in many centers around the world. Chen et al. claimed that treatment with combined continuous venovenous hemofiltration and hemoperfusion significantly improved survival rates.<sup>14</sup> Majority of the studies emphasized that hemoperfusion should be performed within 4 hours of ingestion of paraquat, for best results. However, Ballesteros et al. reported a successful recovery of a pregnant patient with severe paraquat poisoning after 34 hours of exposure, by performing hemoperfusion followed by continuous renal replacement therapy, over 120 hours.<sup>15</sup> Another trial involving 360 patients is underway, which aims to study the benefits of hemodialysis with or without hemoperfusion, in patients presenting with paraquat poisoning.<sup>16</sup>

The current retrospective study by Priya et al. has a relatively large database, compared to the other studies in India, and it focuses on multiple parameters like demography, presentation, organ involvement, treatment vetted, and the outcome. It included 109 patients in a tertiary hospital, where all treatment modalities were provided, including gastric lavage, mechanical ventilation, immunosuppression, antioxidants, hemoperfusion, and renal replacement therapy. The mortality rate despite all efforts, was quite high at 88%, which has been again attributed to late presentation. The study also provides insights on the demographic profile, where 92% of patients belonged to the rural background and a considerable number of patients were in the less than 30 years age group, but these had no relation to mortality. The study also did not find a significant relationship between adjuvant therapy and mortality. Patients presented early did have a better survival chance as reported in earlier studies. Renal replacement therapy did not correlate with a reduction in mortality whereas hemoperfusion, when performed within 4 hours, did provide encouraging results,<sup>17</sup> and does promote its use for managing such cases.

Using certain diagnostic modalities wherever available, like bedside sodium dithionite test, measuring plasma levels, and calculating SIPP score (severity index of paraquat poisoning) for severity and prognosis, can also improve outcome, but this is still to be proved. Maybe, future studies incorporating the above tests and scoring system can provide a better insight.

Despite the multiple measures and modalities available, the high mortality rate of paraquat poisoning continues to be a concern even after 2 decades. Most studies emphasized that late presentation post-exposure is directly related to the bad outcome. However, current reports have shown a ray of hope with the use of hemoperfusion and hemodialysis despite the late presentation of these patients, and these should be applied in all patients till the results of more trials are available. Evidence is lacking regarding the use of other adjuvant therapies, but these continue to be used in the current management, along with supportive treatment. Apart from focusing on the treatment modality, efforts should also be put in to increase awareness amongst the community about the danger of these lethal chemicals, their restricted use, and to avail the medical facility at the earliest, in case of exposure, as a step toward decreasing the overall mortality.

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