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Review Article

Mitigating Oxidative Stress and Lung Fibrosis with Low Dose Radiation Therapy in Paraquat Poisoning: A Case Series

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Abstract: Paraquat poisoning, a frequent cause of fatalities in India, has become a significant public health issue, particularly among farmers. This herbicide, known for its high toxicity, results in severe pulmonary damage, with no specific antidote available. Ingestion of even small amounts of paraquat can lead to rapid multiorgan failure and death, largely due to its accumulation in the lungs, triggering oxidative stress and alveolar fibrosis. The toxicological mechanism involves the generation of free radicals that damage cellular membranes, eventually causing extensive lung fibrosis and alveolitis. Mortality rates remain high, with no definitive treatment. Recent advancements in low-dose radiotherapy (LDRT) have shown promise in treating lung injury caused by paraquat. LDRT's anti-inflammatory properties have been previously explored in non-cancerous conditions like musculoskeletal disorders. Its ability to modulate inflammatory responses in lung tissue suggests potential benefits in mitigating paraquat-induced lung fibrosis. While preliminary evidence from small-scale studies has shown some improvement in patients treated with LDRT, the efficacy remains uncertain. At our center, we have treated five patients using LDRT, with mixed outcomes. Some patients showed improvement, while others succumbed to early pulmonary fibrosis. Further research is needed to establish the role of LDRT in managing paraquat poisoning. Larger studies are required to assess its ability to prevent lung fibrosis and improve long-term survival in patients with severe poisoning.

Keywords: Low-dose radiotherapy, Paraquat, Radiotherapy, Lungs and cellular membranes

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1. INTRODUCTION

1.1. Paraquat poisoning treated with Low dose radiotherapy

In India, suicides due to pesticide poisoning have become a significant public health crisis. Annually, approximately 15,000 farmers end their lives, with nearly half of these cases linked to pesticide ingestion[1]. According to the National Crime Records Bureau (NCRB) 2019 data, around 400,000 farmers died by suicide between 1995 and 2018 which translates to an alarming rate of about one suicide per hour. The number is increasing with a 3.7% rise in 2021[2]. Paraquat, a compound with redox-active properties, belongs to the methyl viologen family[3]. Although it is highly toxic, it does not exhibit teratogenic effects or long-term toxicity. The name "paraquat" is derived from the specific arrangement of quaternary nitrogen atoms within its molecular structure. Due to its redox characteristics, paraquat generates superoxide anions that cause damage to cellular membranes and organelles. While oral ingestion of paraquat is highly toxic, inhalation results in minimal absorption, although it can still lead to severe health issues. Fatalities usually occur within two days of ingesting a 50 mg/kg dose, though death can be delayed for several months at lower doses[4]. The compound's accumulation in lung tissue depletes nicotinamide adenine dinucleotide phosphate (NADPH), produces free radicals, and triggers lipid peroxidation, ultimately resulting in extensive lung fibrosis and diffuse alveolitis[5]. The primary determinant of outcomes in paraquat poisoning is the amount ingested, as indicated by its plasma concentration. While renal failure is commonly observed in patients who survive for longer periods, it is not always a sign of severe illness. The absence of corrosive damage in the upper gastrointestinal tract increases the chances of recovery. Kumar and coauthors [6] (3) found that organophosphate pesticides are responsible for approximately 65% of poisoning cases in India. Although paraquat is widely used in India, poisoning cases are often misdiagnosed as organophosphate poisoning. There is no specific antidote for paraquat poisoning, and the lethal dose is notably low-only 10 mL, equivalent to about two tablespoons. A five-year retrospective study (2014-2018) involving 55 patients at JIPMER revealed a hospital mortality rate of 72.7%[7]. Among the 15 patients who survived, three died two months later due to delayed pulmonary fibrosis. Rao and coauthors reported that 61.4% of 101 individuals affected by paraquat poisoning succumbed to the condition[8]. A 12-year study conducted in the Andaman and Nicobar Islands found that, on average, there were two to five cases per year, all resulting in death. Lung injury was significantly associated with higher mortality rates, even though renal injury did not directly correlate with mortality. Paraquat topically is classified as moderately hazardous (Category III), while oral ingestion is deemed highly toxic (Category II). Inhalation of paraquat is rated at the highest hazard level (Category I), particularly if accidental exposure occurs during the handling or mixing process. Ingestion of less than 20 mg/kg typically results in mild symptoms, but doses exceeding 40 mg/kg lead to severe multiorgan failure and death within two days. Doses ranging from 20 to 40 mg/kg cause serious mucosal damage followed by multiorgan failure, and lung fibrosis often results in the death of survivors within two to four weeks[9]. Since 2007, 58 countries, including those within the European Union, have banned the use of paraquat. In the United States, it is still occasionally used as a pesticide. However, in many developing countries, paraquat remains widely available and is commonly used in agriculture due to its low cost.

1.2. Lung toxicity mechanisms

Pulmonary alveolar cells accumulate polyamines essential for cellular activities. Paraquat, due to its structural similarity to these polyamines, also accumulates in these cells, reaching its peak concentration within a few hours. The distinctive accumulation pattern of paraquat in the lungs may contribute to its specific pulmonary toxicity. The toxicity of paraquat is believed to result from either a reduction in cellular NADP levels or the induction of lipid peroxidation. Histological analysis reveals that lung damage progresses in two stages. The initial stage involves the deterioration of the alveolar epithelium, leading to edema and the buildup of inflammatory fluid. In the subsequent stage, extensive intraalveolar fibrosis occurs as profibroblasts infiltrate, multiply, and differentiate into fibroblasts, mimicking a biphasic response similar to adult respiratory distress syndrome (ARDS). Clara cells, as well as type I and type II alveolar epithelial cells, are the primary cells that absorb the necessary energy for saturated kinetics (Rose and co-authors, 1974). The same mechanism used for paraquat accumulation also facilitates the uptake of various polyamine compounds (Smith, 1982) [10]. Paraquat reacts by transferring an electron, which produces a free radical. This free radical interacts with molecular oxygen to generate a superoxide anion (O2-') and a cation. This oxygen radical can further dismutate to form hydrogen peroxide (H2O2). When Fe++ is present, H2O2 can generate highly reactive radicals like hydroxyl radicals (OH·) (Smith, 1977; Smith & Rose, 1977), leading to lipid peroxidation. Paraquat's redox cycling mechanism reduces H2O2 and lipid hydroperoxides, as well as NADPH levels. Extended periods of reduced NADPH can damage cells and increase their susceptibility to oxidative stress and the oxidation of critical physiological components. This ultimately leads to acute alveolitis following the loss of alveolar epithelial cells. Damage to the alveolar structure that leads to extensive fibrosis can cause severe hypoxia, which may be fatal. The early stages of fibrotic changes, including whether they affect the interstitial or intraalveolar regions, are not completely understood.

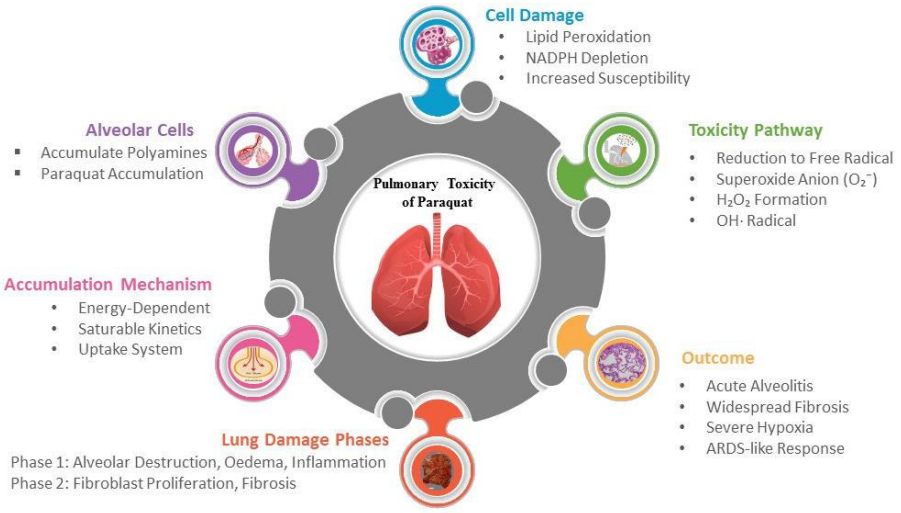

Fig 1: Pulmonary Toxicity of Paraquet

2. TREATMENT

When addressing this type of poisoning, the initial step is to eliminate as much of the toxin as possible, using agents like Fuller's earth, activated charcoal, or gastric lavage. Treatment usually involves antioxidants or hemodialysis to address the effects of the poison. Utilizing antioxidants, along with cyclophosphamide and steroids, can help counteract damage caused by free radicals. Oxygen therapy should be administered only if the SpO2 falls below 92%, as excessive oxygen could potentially worsen lung damage. Despite the best treatment efforts, the mortality rate remains high, between 70% and 90%.

2.1. Role of Radiotherapy

In recent years, the application of radiation therapy (RT) has expanded to include non-cancerous conditions, demonstrating its innovative potential. Low-dose radiation therapy (LDRT) has been shown to be effective in treating pain associated with musculoskeletal disorders due to its anti-inflammatory properties[11]. It has been shown to benefit conditions such as osteoarthritis (OA) in various joints, plantar fasciitis, trochanteric bursitis, and other tendinopathies. Recent research in radiobiology has revealed that LDRT reduces inflammation by affecting various inflammatory pathways and cellular components, including macrophages, leukocytes, and endothelial cells. LDRT influences macrophages through the nitric oxide pathway by inhibiting the production of nitric oxide via inducible nitric oxide synthase. Additionally, while higher doses of radiation (above 1 Gy) tend to drive macrophages towards a proinflammatory M1 phenotype, lower doses (below 1 Gy) encourage an anti-inflammatory M2 phenotype. Studies have also shown that LDRT at doses between 0.3 and 1.0 Gy affects endothelial cells by reducing leukocyte adhesion and migration. Moreover, LDRT can lower the production of proinflammatory cytokines by leukocytes and accelerate their apoptosis. Evidence from both clinical studies and animal models supports the anti-inflammatory effects of LDRT, with effective results observed at cumulative doses ranging from 2.5 to 7.5 Gy and single doses between 0.5 and 1.5 Gy[12-14]. According to Meziani and coauthors, interleukin-10 (IL-10) is a key factor in mediating the anti-inflammatory effects observed in influenza-induced pneumonia, with this cytokine produced by macrophages associated with neural and airway tissues after low-dose radiation therapy (LDRT). In the early 1900s, X-ray therapy was employed to treat pneumonia, with the first recorded use by Musser and Edsall in 1905. Follow-up studies involving approximately 700 cases of pneumonia demonstrated that small doses of X-rays could effectively lead to disease remission. Given the high mortality rates and limited treatment options during the COVID-19 pandemic, the potential of LDRT was re-evaluated. In a previous study conducted at our institute, 51 patients with RT-PCR positive COVID-19 presenting between November 2020 and July 2021 were allotted to receive 0.5 Gy single session LDRT along with standard pharmacologic therapy (34 patients) versus pharmacologic therapy alone (17 patients). All patients had SpO_2 <94% at presentation. LDRT showed a statistically significant early improvement in oxygenation ($p < 0.001$), an early time to clinical recovery (4 versus 11 days in intervention and control) ($p < 0.001$), early hospital discharge ($p < 0.001$) and better radiological resolution ($p = 0.011$) compared to control group. The 28-day mortality rate was 14.7% in LDRT group versus 23.5% in controls but statistical significance could not be proved, probably because LDRT subjects had worse baseline CT severity scores and higher comorbidities than control group[15]. A 2022 systemic review involving 61 patients from two of four trials showed improvements in inflammatory markers. The drawback of using of LDRT in COVID-19 might be attributed to the cytokine storm phenomenon. In 1984, Webb and colleagues from Cambridge were the first to document the use of low-dose radiation therapy (LDRT) for treating lung damage caused by paraquat poisoning[16]. The patient received a total dose of 11.25 Gy, administered in five daily fractions, alongside other supportive measures. Although the patient did not show symptoms, follow-up assessments revealed persistent impairment in lung function. By 1987, Webb and team reported on four additional cases. After receiving oxygen therapy-shown to be harmful in animal studies all four patients developed symptoms of elevated plasma paraquat levels and difficulty breathing within four days. Each patient eventually succumbed to renal and liver failure in addition to respiratory complications. Nonetheless, two of these patients showed temporary improvements in their clinical and radiological conditions following radiation treatment. The total radiation dose of 11.5 Gy was delivered in daily fractions, with each lung receiving a different fractionation schedule. This was calculated to be two-thirds of

the lung's tolerance dose (22.5 Gy in 15 fractions), based on the approach outlined by Wara and coauthors, ensuring a significant margin of safety. Webb and colleagues indicated that patients with a favorable prognosis-defined by Proudfoot and coauthors (1979) as having a plasma level exceeding 0.6 mg/L at 6 hours-might benefit from radiation therapy. On the other hand, for individuals with severe poisoning and considerable alveolar damage leading to early lung symptoms, radiation therapy is unlikely to be effective.

2.2. Institutional Experience

At our centre (Harshamitra Cancer and Multi-Speciality Hospital, Trichy, India), we have treated a total of 5 patients so far, ranging from ages 15 years to 29 years. LDRT dose of 1 Gy/single # was delivered to both lungs 6MV (AP PA fields) in Varian Unique Linac. RT was delivered at Day 2 for 2 patients and Day 4 for other patents. On Follow-up two patients have recovered completely. Two patients have died. One is lost for follow up. The 2 pts who died had dyspnea and Sp02 91-92% at presentation and CT findings of Early pulmonary fibrosis. In addition, one of them had AKI (Urea 150 mg/dl) and clinical jaundice and received Hemodialysis thrice. For the 2 patients who died, RT was initiated at Day 2 and Day 4 respectively. Inspite of treatment, they expired within 2 months. Poor prognostic factors like Early onset pulmonary fibrosis might be the reason for the treatment failure in these cases. The two patients who are alive were stable at presentation. One of them had Early Onset Pulmonary fibrosis on CT and mild derangement of RFT and LFT, which resolved post RT. In this patient RT was initiated early on Day 2. The other patient did not develop fibrosis. Both patients are alive at 1-2 months. Several other patients have received irradiation at centres throughout the world, but none has been reported in the literature.

3. DISCUSSION

Various approaches have been explored for preventing lung fibrosis, drawing from a small number of animal and human studies. Despite this, many trials have not demonstrated significant benefits (Pasi, 1978). Research conducted in the West Indies has indicated that high doses of cyclophosphamide and dexamethasone may reduce mortality in patients with paraquat poisoning (Addo & Poon-King, 1986). The use of lung irradiation to prevent fibroblast proliferation remains a topic of debate. While it shows promise in treating severe poisoning cases, its effectiveness for patients with uncertain prognoses is still undetermined (Savy and co-authors, 1988; Talbot & Barnes, 1988; Williams & Webb, 1987). Additionally, there have been suggestions to use inhibitors of collagen synthesis, colchicine, and nonsteroidal anti-inflammatory drugs to prevent lung fibrosis. However, human studies have not supported these recommendations (Akahori & Oehme, 1983; Pasi, 1978; Shahar and co-authors, 1989; Vincken and co-authors, 1981). In a 1987 study conducted by Talbot and co-authors. in Taiwan, a 17-year-old female ingested 15 milliliters of 24% paraquat[17]. Her plasma concentration was recorded at 2.1 mg/L, which is significantly higher than the critical survival threshold of 0.6 mg/L as defined by Proudfoot and co-authors. According to survival probability data from Hart and co-authors. (1984), this level indicated a 15% chance of survival. Radiation therapy was administered starting on the third day, with a total of 11.25 Gy given in five fractions to each lung using AP-PA portals. By the sixth day, evidence of kidney and liver damage was observed. On the eighth day, chest X-rays indicated decreased arterial PO2 and worsening lung infiltrations. By the twelfth day, the right lung also exhibited infiltrations. However, by the seventeenth day, the patient's blood gases had normalized, and by the twentieth day, most of the infiltrations had resolved. Follow-up a year later revealed no scarring in the lungs. In a subsequent 1988 study by Talbot and co-authors., adjustments were made to the radiation therapy protocol based on updated chest X-ray findings for cases 8 and 9. Treatment commenced on the second day delivering a total dose of 12.50 Gy in 10 fractions of 1.25 Gy each, while sparing the mediastinum as much as possible. Follow-up showed interstitial infiltrates in cases 1, 5, 6, and 8, pulmonary edema in cases 7 and 9, and clear chest X-rays in cases 2 to 4. Of the eight cases treated, five patients survived, including the first five and the sixth. In Case 8, interstitial infiltrates persisted for three months before resolving. While evidence is limited, radiation therapy may have potential benefits. The survivor in this study had a plasma paraquat level of just 0.68 mg/L, indicating an exceptionally low initial concentration. In 1987, Masashi Shirahama and team documented a case involving a 51-year-old man from Japan who ingested fifty milliliters of paraquat mixed with an organophosphate insecticide[18]. Blood tests showed paraquat levels below 2.5 micrograms. Radiotherapy was started on the fifth day and lasted for six days, delivering a total of 960 rad (160 rad per day for 6 days) to each lung using 4 MV radiation. By Day 7, the chest X-ray results indicated a rise in PaO2 levels, reaching 84 mm Hg by the end of the treatment on Day 17, which suggested that the pneumonia was improving. In a 1991 study conducted by Damian Franzen and colleagues, a 23-year-old man who consumed 8 grams of paraquat experienced a peak serum concentration of 2.5 mg/L, which soon dropped to 0.3 mg/dl[19], below the critical level of 0.6 mg/dL. By the third day, his respiratory condition worsened, necessitating mechanical ventilation. Radiological images showed early onset bilateral lung opacities. Radiation therapy was administered on Day 5, with a total dose of 14.4 Gy given in 1.8 Gy fractions over five days. Despite the treatment, the patient succumbed to his condition fifteen days later. This case illustrates the importance of initial paraquat levels and early initiation of RT for improving survival chances.

3.1. Timing of RT

Radiotherapy was initiated on various days based on chest radiography changes: Day 4 (Webb and co-authors., 1984), Day 4 (Bloodworth and co-authors., 1986), Days 4 or 5 (Williams & Webb, 1987), and Day 7 (Chou and co-authors., 1987). SEM studies indicated that alterations in alveoli appeared in mice within 48 hours of paraquat exposure, with fibroblast accumulation becoming noticeable five days later (Torre and co-authors., 1984) [20]. If low-dose radiation therapy (LDRT) begins after significant pulmonary function decline, fibroblasts might have already begun collagen deposition (Williams & Webb, 1987). By the third day, although the patient had been tachypneic previously, the chest radiograph showed favorable results. In addition to radiation, patients received prednisolone and vitamin C. Fractionation of radiation allows repair of sublethal damage between doses. Prednisolone, given in advance, can reduce radiation pneumonitis and potentially mitigate membrane damage caused by paraquat (Gross, 1977). Evidence of radioprotection has been observed in vitro (Stratford & Hodgkiss, 1986)[21], and high doses of vitamin C have been proposed as a treatment for paraquat poisoning (Halliwell, 1976).

3.2. Radiation dose

Gross (1977) estimated that administering a total dose of 11.25 Gy to each lung, spread across five sessions over 11 days, would result in a biological effect of 587 ret. This dose is notably below the lung's tolerance due to paraquat's radiosensitizing properties (Wara and co-authors., 1973; Gerard and co-authors., 1984). The study by Webb and co-authors. in 1984 indicated that a dose of 656 ret to the right lung led to a quicker response. After a single 2.25 Gy treatment, survival rates drop to just 10%, according to Webb and co-authors. and Weichselbaum and co-authors. (1976). Cox and co-authors. (1978) found that reducing fibroblast levels to 37% requires a dose between 0.9 and 1.5 Gy. Research has shown that the entire lung can tolerate radiation. Safe doses, such as 22.5 Gy delivered in 15 fractions, have been used for treating Wilms tumor and lung metastases. Clinical trials employing 19.5 Gy in 13 fractions and 17.5 Gy in 10 fractions reported no adverse effects. The literature also covers the use of high doses of X-rays for total or partial body irradiation in bone marrow transplants and palliative care, with no significant late-onset toxicity or pneumonitis observed. Webb and co-authors. monitored for 14 months, assessing lung function, chest X-rays, blood gases, and spirometry, finding no signs of long-term radiation fibrosis.

3.3. Prognostic markers

The outcome of paraquat poisoning is largely determined by the concentration of paraquat in the plasma, which can be quantified using radioimmunoassay methods. This measurement is strongly linked to the severity of the patient's condition. For samples obtained within the first 24 hours, concentrations above 2 mg/L at 4 hours, 1.6 mg/L at 12 hours, 0.6 mg/L at 16 hours, and 0.16 mg/L at 24 hours are considered fatal. Scherrmann and colleagues (1983, 1987) have shown that this correlation holds true for up to ten to eleven days following exposure. Bismuth and co-authors. (1982) highlight that key factors include both the concentration of paraquat in the herbicide and the amount ingested. The most reliable methods for obtaining this information are through a comprehensive review of the incident report or direct examination of the container and its contents. Additionally, the interval between paraquat ingestion and the last meal may be relevant, as food can absorb and partially neutralize the toxin. The presence of stomach and esophageal ulcers within 24 hours of ingestion signifies acute poisoning, while the absence of ulcers suggests a less severe outcome. Bismuth and co-authors. (1987) also found a significant negative correlation between the amount of paraquat removed by hemodialysis or hemoperfusion and patient survival time. Effective removal of paraquat from circulation leads to higher retention in tissues, increasing the risk of early mortality. The timing between an emergency department visit and the start of hemoperfusion (HP) is a critical factor in determining the treatment outcome. Bloodworth and co-authors. (1986) observed a patient whose paraquat ingestion was assessed 7.5 hours later, with serum levels recorded at 0.98 mg/L. Despite these relatively low levels, HP did not commence until 36 hours' post-ingestion, resulting in suboptimal results. In contrast, Chou and co-authors. (1987) reported a patient who underwent five HP treatments within the first two days, although detailed clinical data and paraquat serum levels were not available. A comprehensive case report should provide a detailed analysis of the entire treatment approach.

4. CONCLUSION

In view of limited options and poor prognosis and well established role of RT as an immunomodulatory agent, further larger studies or prospective studies are required to draw definitive conclusions on benefit of RT in alleviating lung damage in paraquat poisoning. The effectiveness of RT in preventing lung fibrosis and ARDS in specific patient populations remains uncertain, though it could potentially improve long-term survival and quality of life.

5. AUTHORS CONTRIBUTION STATEMENT

All authors are equally contributed.

6. CONFLICT OF INTEREST

Conflict of interest declared none.

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