Paraquat Poisoning and the Salvage Treatment

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Abstract: **The overall purpose of the study is to know the various medications used for the treatment of paraquat poisoning, as there is no perfect treatment. Lomorin, upon adding the anticoagulants to current therapy along with silymarin shows better improvement in patient's health. Paraquat is a herbicide, widely used in agriculture. The toxicity and severity depend on exposure, dose (in case of suicidal intake), and initiation of the treatment. The emergency cases are considered regardless of COVID (status). The results reported are 38.8% (7 out of 18) of deceased patients. The symptoms are oral ulcers (66%), dysphagia (50%), dyspnea and vomiting (44.4%), icterus (33%). In 61.1% of patients improved condition is noticed, those who received low molecular weight heparin along with other medications like vitamin C,E, ambroxol, ondansetron, mucaine gel, methylprednisolone, and silymarin. There are many reasons that lead to consumption, like self poisoning, accidental consumption, and psychological issues; mainly the young people are affecting more. Due to lack of proper antidote, the worsening of symptoms occurs and the patients are treated symptomatically. Based on the dose intake, the severity differs. The initial treatment includes gastric lavage, stomach wash but should not induce emesis. As multi organs are affected, proper care must be taken, especially in case of lung tissues, once they are affected and if not treated that leads to ARDS and then lung fibrosis. In case of renal failure, dialysis is preferred; silymarin shows promising results in treating PQ-induced nephrotoxicity. Likewise, corticosteroids and anticoagulants like Lomorin show good results in improving lung functions. Combination therapy is mostly prescribed and regular follow up is needed, even after the recovery of the patients as post treatment complications are more and may even cause death of the patient.**

Keywords: **paraquat poisoning, lomorin, silymarin, treatment of PQ poisoning.**

I.INTRODUCTION:

The challenge of ensuring food security for a large population and prohibitive cost of manual clearance of weeds in India has made chemical clearance of weeds with herbicides, such as paraquat, a necessity in agricultural practice **[3].** Paraquat (PQ, 1,1′-dimethyl-4-4′-bipyridinium dichloride) is a highly toxic quaternary ammonium herbicide widely used in agriculture as a non-selective herbicide and a potent toxin.[1] In India, it is permitted for use by the Central Insecticide Board and registration committee and is available as a 24% concentrated solution.[15, 27] It is often sold without the need for prescription by agricultural officers. Applicators are untrained and store it in easily accessible conditions. Just 10 ml of paraquat can kill a human if ingested and mortality ranges from 50% to over 80%.[23, 26 ,28]

Ingestion, rather than inhalation, is the typical route of exposure associated with human toxicity. There have been systemic reactions following skin exposure after direct exposure to the skin (e.g., soaking of the skin with paraquat) or when the skin integrity has been breached (e.g., preexisting skin lesions or burns).[1] Suicides due to paraquat (PQ) are an important cause of morbidity and mortality, especially due to the absence of specific antidote..The mortality rate of PQ poisoning is as high as 60–80%, mainly due to acute lung injury and progressive pulmonary fibrosis [7]. Consumption of PQ > 40 mg/kg causes acute multi organ failure with death within the first 2 days, while < 20 mg/kg of PQ causes mild symptoms and most survive. Paraquat of 20–40 mg/kg causes severe mucosal damage followed by multi organ failure. The few, who survive, die within 2–4 weeks due to lung fibrosis. The pulmonary alveolar cells selectively accumulate polyamines that are required for cellular functions. Being structurally similar to polyamines, PQ gets accumulated in these cells, causing selective delayed lung injury[8].The mechanism of paraquat toxicity is attributed to the generation of superoxide radicals that may be partly iron dependent damage the cellular organelles and membranes, causing damage to many organs, especially the pulmonary alveolar epithelium[8]. Consistent with an oxidant mechanism, supplemental oxygen and radiation therapy may worsen the outcome.[1] Clinical signs of acute paraquat poisoning include diarrhea, vomiting, and ulceration of the oral and gastrointestinal tracts. In all cases of severe poisoning, acute respiratory distress develops because of pulmonary edema. Days to weeks after exposure, progressive respiratory insufficiency occurs because of severe pulmonary fibrosis. Although paraquat ingestion leads to acute gastrointestinal tract necrosis and multiorgan failure, the lung is the target organ for toxicity and patients usually develops pulmonary edema with high dosage (paraquat>40mg/kg), observed 24 to 48 hours after ingestion among those surviving the immediate post ingestion period. The pulmonary edema may evolve to a condition resembling ARDS, which may progress to an accelerated, chemically induced pulmonary fibrosis[1].There are no known antidotes for paraquat poisoning, and enhanced elimination such as by hemoperfusion has not demonstrated a clear benefit. Paraquat is absorbed quickly, within 2 hours pulmonary tissue paraquat levels are 5 times greater than serum levels, which limits the efficacy of the usual decontamination techniques, although activated charcoal should be administered for presentations within 1 hour of ingestion; paraquat-induced caustic injury is not usually noted for many hours post ingestion [1]. Most patients receive steroids/cyclophosphamide/antioxidants to reduce free radical damage [8].The lung injury in paraquat poisoning group increased with exposure period, the lung fibrosis in anticoagulation therapy group was lower than that in paraquat poisoning group (without anticoagulation) .A variety of clinical studies have shown that high-dose ambroxol can alleviate the lung damage caused by PQ poisoning and enhance the effect of therapy for PQ poisoning.[9]. Paraquat-induced renal toxicity is highly common and reported as the first systemic effects of the paraquat toxicity. A rapid increase in serum creatinine level has been observed in previous reports

of paraquat toxicity, which indicates a decrease in kidneys glomerular filtration rate (GFR). Paraquat causes impaired renal function which is accompanied by reduction of the renal clearance rate and increasing of paraquat level, toxicity, and other organ dysfunctions [16].Anticoagulation therapy can improve hypercoagulation state and acute lung injury in rats induced by paraquat poisoning [26].Thrombotic microangiopathy was recently elucidated as the primary systemic pathological event in PQ poisoning, but antithrombotic drugs have never been tested. Here, we describe the unexpected survival of patients with severe PQ poisoning after adding enoxaparin to his treatment [10]

II.METHODS

Inclusion and exclusion criteria:

We collected the data from January 2021 to November 2021 and during the period, 18 emergency cases were admitted to hospital due to poisoning and aged between 16 to 41 years. We included consecutive patients with paraquat poisoning. Excluded the patients infected with COVID and immediate deaths with very severe poisoning above 200ml.

Data collection:

We collected the patient demographics, clinical presentations, laboratory data and clinical follow-up from the medical charts. For surviving patients, we follow up for a few months. We have taken consent from the patient and their relatives while collecting the data and medicating them.

III. RESULTS

In this study we considered 18 patients whose age groups ranged between 16 to 41years and who wantedly consumed the paraquat were admitted to hospital. In the admitted patients males and female ratio was 15:3 and total death percentage was 38.8% (7 out of 18) and in the deceased patients 28.5% were female (2 out of 7) and remaining 71.4% were males (male and female mortality ratio 2:1) . In these, patients were dead due to cardiac arrest and delayed admission to hospital though receiving the proper treatment couldn't make it possible. The clinical signs commonly noticed in the admitted patients were oral ulcers (66%), dysphagia (50%), dyspnea & vomiting (44.4%), icterus (33%) and other symptoms were oliguria, epigastric pain, congested buccal mucosa in some of the patients. The patients who received low molecular weight heparin along with other medications like vitamin C, E, ambroxol, ondansetron, mucaine gel, methylprednisolone, silymarin and improved their condition were 61.1% and deceased were 38.8%.

IV.DISCUSSION

The major finding in this study is the usage of low molecular weight heparin through subcutaneous route and silymarin given through orally for the patients who consumed the paraquat. There was a productive outcome in many cases. Along with the heparin or anticoagulant therapy, the patients were given corticosteroids, ambroxol and for treating the oral ulcers, gels like mucaine gel and in some cases if it was fungal infection given fluconazole. The kidney impairment developed due to consumption of paraquat underwent dialysis, and silymarin showed improvement in their condition, and also vitamin C 5g/day reversed kidney injury. Vitamin C reversed Kidney injury even without dialysis in some cases with fluid management. We observed in our study that the common reasons for self poisoning of paraquat were psychiatric problems, alcohol consumption and also personal issues which they couldn't face by themselves and committed to suicide. Some authors in their study mentioned about the reasons behind suicidal ideations leads to consumption of paraquat were generally like poverty, diminished wealth [3, 11, 17, 21].The clinical manifestations mainly included nausea, vomiting, aphthous stomatitis, weakness, lethargy, oral canker sores, painful lesions, tongue and throat redness, jaundice, dyspnea, bilateral crackles, tachypnea, fever, sialorrhoea, pupil mydriasis, oral and lips burns, body pain, and digestive problems before causing systemic effect, this results in mild to toxic liver and kidney effects [4, 19, 24]. According to Shadnia S *et al.,* for primary poisoning diagnosis the odor perception was needed.[19] This intoxication was mainly observed in the young and middle aged people including 16 to 41 years of age who consumed >20mg were immediately affected and were rushed to hospital [4, 10, 20]. Asisha Janeela *et al.,* mentioned in their study that PQ intoxication affect healthy Colombian men ranging in age from 15 to 44 years and the ingestion of > 40 mg PQ ion/kg of body weight results in early death (24–48 hours) from multiple organ failure, and was considered as fatal dose of paraquat intake[4, 10, 20]. Mohammad Delirrad *et al.,* reported that < 25ml of paraquat intake had shown good prognosis in patients, in some cases it is irrespective of dose intake [22]. Shahin Shadnia *et al.,* stated that the fast-acting nature, stability, availability, and affordability, and the lack of effective treatment, make PQ an extremely hazardous substance [19].The initial treatments performed in most of the patients were gastric lavage, stomach wash. Few authors Yun-fei Jiang *et al.,* Harika Cherukuri *et al.,* mentioned in their study that performing gastric lavage within 1 to 6 hours might help the patient to recover in case of acute poisoning[13, 24]. Chinese expert consensus documents on acute PQ poisoning diagnosis and treatment recommend that gastric lavage should be performed within 4–6 hours of PQ ingestion [13]. Inducing emesis is not recommended instead gastric lavage might be helpful when performed within 1 hour of ingestion, although it may be useful up to 24 hours after ingestion.[24] Shahin Shadnia *et al.,* mentioned in their study that there were different clinical manifestations based on the amount which ranges from 20mg to 40mg paraquat ion per kg BW and on the severity and complications leads to mild poisoning to respiratory failure and to death [19]. M. Asisha Janeela *et al.,* stated that the route of administration , the point of contact also gets affected like oral ingestion can lead to erosions of the tongue, oral mucosa, and corrosive injury to the GI tract with poison dose <20 mg/dl. In our study one young girl aged 16 years died after 4 days with severe oral ulceration including tongue without renal hepatic and pulmonary injury and manifestations. Renal tubular necrosis, hepatic necrosis, and pulmonary fibrosis can be seen with moderate toxicity with consumption of 20–50 mg/dl where death usually occurs in 2–3 weeks. And here the poisoning was completely dose dependent [20].Archana Dambal *et al.,* supported this statement that the rate of improvement or survival depends on the diagnosis, initiation of the treatment [3].

Lack of antidote, need for expensive healthcare, resulting burden on the family's economy and high mortality reflected the enormity of this disease in our patients. And there is also no specific treatment for paraquat poisoning [3, 9, 17, 19].

There are some complications reported in patients while receiving the treatment like, developing oral infections, ulcers. Later on these got relieved upon using the appropriate medications. The deteriorated condition includes dyspnea and hypoxia that requires urgent attention and oxygen therapy in case of ARDS. The toxicity usually depends on the dose of paraquat administered and organs affected; if it involves the lung tissues and not treated it may lead to ARDS. Senthil Kumar *et al.,* stated in their study that there are often diverging interpretations of the morphological changes induced by paraquat poisoning due to the differences in experimental design, species used, the dose and route of paraquat administration, and the time interval of exposure [5]. Yanfei Shen *et al.*, mentioned in their study that a decreased urine output may indicate low renal perfusion and consequent fluid overload, which in turn contributes to subsequent organ dysfunction [12]. In our study most of the deceased cases were due to decreased urine output, hypoxia deteriorating rapidly, pulmonary arrest and hepatopulmonary syndrome. The hepatopulmonary syndrome usually develops after 3 to 4 weeks manifesting as sudden hypoxia in upright position or after taking few steps or walking few meters and death. The treatment for hepatopulmonary syndrome generally includes pentoxifylline (400mg), norfloxacin (400mg), quercetin , antioxidant chemical in fruits of Jatropa, scientific name of sapota fruits 4/shift and also caffeine (coffee 1-2cups/day)can be given for 1 to 2 months. Dialysis was performed in a few cases and some people recovered after the treatment. Mohammad Delirrad *et.al.,* stated in their study that important variables for the high fatality rate of paraquat intoxication in their study were a large amount of ingested volume, prompt vomiting, loss of consciousness, need to ICU admission on entrance, leukocytosis, initial appearance of respiratory, hepatic or renal failure, development of severe hypotension or cardiogenic shock and need for infusion of vasopressor agents [22].
Treatments including oral Fuller's earth, forced diuresis, hemofiltration, corticosteroids, *N*-acetylcysteine (NAC), methylprednisolone, cyclophosphamide, vitamin E, colchicine, and nitric oxide (NO) inhalation, immunosuppressive therapy like, pulse steroids and cyclophosphamide were investigated and positive outcomes were seen in PQ-intoxicated patients.[4, 19 ,20,24]. N-acetyl cysteine was used in a few cases, as there was no particular antidote for the paraquat poisoning. In our study patients were given 60ml doses of ambroxol, BD and better response was observed. Junwu Wang *et al*. mentioned in their study that high-dose ambroxol has a therapeutic effect on ALI and acute respiratory distress. So, in such cases it can be used in paraquat poisoning [9].
Paraquat-induced nephrotoxicity is a common cause of mortality in this group of patients. The antioxidant properties of silymarin produce protective effects against kidney damage through reducing the inflammatory factors such as TNF-α[16] .
Zakaria Zakariaei *et al*., in their study mentioned the protective effect of Silymarin against PQ-induced cytotoxicity on human lung adenocarcinoma cell line[14].Some results of animal studies by C Jia *et al.*, proved that silymarin has antioxidant activity with therapeutic potential for the treatment of PQ-induced acute kidney damage and was given (100 and 200 mg/kg body weight) for 3 days could effectively reduce PQ poisoning related death. At the physiological level, silymarin treatment was able to alleviate PQ-induced elevation of serum creatinine, BUN.[2]
According to a few authors, Shahin Shadnia *et al.*, M. Asisha Janeela *et al.*, Paraquat is a bi pyridyl compound which causes direct cellular damage by production of superoxide radicals or other reactive oxygen species and nitrite radicals. Because PQ-induced reactive oxygen species (ROS) and oxidative stress (OS) events and inflammation are underlying various molecular mechanisms, thus antioxidant such as acetylcysteine and salicylate, as scavenging of free radical, anti-inflammatory and NF-κB inhibitory effects and immunosuppressants such as dexamethasone, cyclophosphamide (CP) and methylprednisolone (MP) were applied[19, 20]. Jie Gao *et al.*, in their study said that the results showed that prolonged low-dose MP treatment improves lung function in patients with mild PQ poisoning [18]. Patients receiving prolonged treatment had better lung function 2 to 3 months after PQ poisoning. But to our patients we recommend a high dose of steroids (2g/day initially for first 2 days then 1g/ day) and later taper the dose every week by 25%, this shows better improvement in the patients. In some studies they recommended the anticoagulant drug therapy, especially lomorin for treating the poisoned cases, and so do we and it showed promising results in a few patients, as some were unable to recover because of some complications. It is increasingly recognized that low-molecular-weight heparins (LMWH) have many pharmacological properties beyond their anticoagulant activity. The main finding was that pulmonary thrombotic microangiopathy was the primary pathological event in PQ poisoning characterized by alveolar capillary thrombosis, atelectatic changes, destruction of alveolar walls, rupture of subpleural alveolar walls and emphysematous changes. Therefore, the potential for antithrombotic drugs in severe cases deserves to be tested. First, enoxaparin has more predictable pharmacokinetics than unfractionated heparin (UFH), and it has been used extensively in intensive care units, requiring a subcutaneous daily dose of 60 mg [10]. M. Asisha Janeela *et al.*, along with the treatment, proper follow up is required so as to reduce the mortality rate as there might be a chance of development of delayed mortality due to lung fibrosis. The outcome depends on the severity of the poisoning and the time taken to avail medical help. The reasons why our patient survived could be because of the quantity of poison taken, the lack of acidosis, and the good supportive treatment that was given [20].
Our results have shown that lomorin, silymarin, methylprednisolone, ambroxol, high dose vitamin C and other supportive treatments have shown positive results and improvement in health conditions. Regular follow up of patients (post treatment) is required for few months. In life threatening cases, the dialysis is performed immediately after the ingestion of paraquat.

V.CONCLUSION

The Lomorin, anticoagulant along with other supportive medicines will show effectiveness in paraquat poisoning and proper follow up and observation is needed more. Treatment without proper follow up may result in death of the patient.

VI.ABBREVATIONS

PQ- Paraquat, BW- body weight, ALI- acute lung injury, ARDS- acute respiratory distress syndrome.

VII. ACKNOWLEDGMENT

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