Effectiveness of Extra Corporeal Removal Methods in the Management of Paraquat Poisoning: A Retrospective Analysis

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Abstract

Paraquat poisoning is a major medical problem in many parts of Asia, Pacific nations, and America. An increased rate of morbidity and mortality is associated with paraquat poisoning due to the absence of a definite antidote. The objective of this study is to assess the effectiveness of various treatment strategies with the outcome in paraquat poisoning. In this study the mean age of 206 patients were 28.14±11.35 years. Majority of the patient population were males (63.6%). Extra Corporeal Removal treatment (ECR) (45.6%) method was given majorly to the patients. Primary outcome analysis with respect to various ECR methods revealed that hemoperfusion (43.9%) showed better results compared to other ECR methods. Secondary outcome such as the ICU days (4.66±3.43), ventilator days (0.63±1.61), and secondary complications (7.6%) was comparatively less in the group treated with hemoperfusion. The treatment analysis revealed ECR of Paraquat by hemoperfusion ensured better clinical outcomes in terms of primary and secondary outcomes.

Introduction

Paraquat also known as Methyl Viologen is one of the most widely used herbicides. It is fast-acting, non-selective, kills green plant tissue on contact. It is toxic to mammals due to its redox activity, which produces superoxide anions, causing more than 50% case fatality rate. A large majority of fatalities from paraquat poisoning are suicides, which occur mostly in developing countries, whereas the greatest risk of accidental poisoning is during mixing and loading paraquat for use. The most common route of poisoning is through ingestion (toxic), other routes like dermal or mucus contact (moderately toxic), and inhalation (highly toxic) or injection have also been reported [1].

Self poisoning poses a major public health problem in developing countries, around 300,000 deaths occur in Asia-Pacific each year.[2] Ingestion of paraquat causes symptoms such as liver, lung, heart, and kidney failure within several days to several weeks that can lead to death up to 30 days after ingestion. The alveolar epithelial cells of the lung selectively concentrate paraquat, potentially leading to Acute Respiratory Distress Syndrome (ARDS) [2].

Although there are no specific antidotes, initial gastrointestinal decontamination with fuller's earth or activated charcoal is an effective treatment if taken in time, followed by steroids and immunosuppressive agents like cyclophosphamide, dexamethasone and methylprednisolone, antioxidants like N-Acetyl Cysteine (NAC), vitamin C, vitamin E and extra corporeal methods (ECR) like haemodialysis (HD), hemoperfusion (HP), and hemofiltration (HF) [2]. However, evidence with efficacy and safety of the general treatment for Paraquat poisoning is not available but most of the study support HP and administration of NAC [1].

There is no proper well-established treatment protocol available in the literature which suggests the effective management of paraquat poisoning [3]. However, in recent studies use of ECR methods like HP and HF showed some positive outcome, when compared to the conventional treatment [4, 5]. This study

tries to provide evidence for the existing data to support the most efficient strategies to improve the outcome in paraquat poisoning.

Results

Demographic characteristics. The study included 206 patients that were admitted to the emergency department between 2012 and 2019 with paraquat poisoning. The study comprised of 131 (63.6%) males and 75(36.4%) females. The mean age of the study population was 28.14±11.35 years. Among the study population, 60(29.1%) patients were alcoholics and 28 (13.6%) were smokers. Majority of the cases were found to be suicidal 199 (96.6%). Psychiatric illness was found in 23(11.2%) of the patients and 15(7.3%) patients had chronic illness during the treatment for paraquat poisoning. The major clinical symptoms were observed to be vomiting (55.8%), followed by oropharyngeal burns (29.1%). Majority of the patients were admitted within or less than 12 hours (55.8%) to the hospital after consumption of paraquat poison. Further demographic details of the population are given in Table 1.

Variables	Frequency
Mean Age ± SD in years	28.14±11.35
Gender	
Male, n (%)	131(63.6%)
Female, n (%)	75(36.4%)
Social habits	
Alcoholic, n (%)	60(29.1%)
Smoking, n (%)	28(13.6%)
Type of Exposure	
Suicidal, n (%)	199(96.6%)
Accidental, n (%)	7(3.4%)
Comorbidities	
Psychiatric illness, n (%) Depression, n (%) Personality disorder, n (%) Others, n (%)	23(11.2%) 10 (4.86%) 9 (4.38%) 4 (1.94%)
Chronic illness, n (%) Cardio vascular disease, n (%) Hepatic dysfunction, n (%) Acute kidney injury, n (%) Sepsis, n (%) Seizure, n (%) Anemia, n (%) Steroid induced T2D, n (%) COPD, n (%)	15(7.3%) 3 (1.46%) 2 (0.96%) 2 (0.96%) 2 (0.96%) 2 (0.96%) 2 (0.96%) 1 (0.48%) 1 (0.48%)
Clinical Presentation	
Oropharyngeal burns	60(29.1%)
Vomiting	115(55.8%)
Abdominal symptoms	12(5.8%)
Vomiting + Abdominal symptoms	23(11.2%)
Other symptoms	106(51.5%)
Poison severity score	
None	9(4.4%)
Minor	40(19.4%)
Moderate	29(14.1%)
Severe	27(13.1%)
Fatal	101(49%)
Time of hospitalization	
No hospitalization	37(18%)
≤12 hrs	115(55.8%)
≥12 hrs	54(26.2%)

T2D: Type 2 diabetes; COPD: Chronic Obstructive Pulmonary Disease.

Table 1. Demographic characteristics of the patients admitted to an Indian tertiary care teaching hospital with Paraquat poisoning between 2012 and 2019. (N=206)

Treatment for Paraquat poisoning. General management includes various treatment and combinations of treatment patterns as depicted in the Table 2.

Treatment	Frequency, n (%)
I.V Fluids	205(99.5%)
PPI	204(99%)
NAC and other antioxidants	77(37.4%)
Steroids and Immunosuppressant	85(41.3%)
Antibiotics	128(62.1%)
NAC+Steroids	57(27.7%)
Activated Charcoal	24(11.7%)
Gastric Lavage	97(47.1%)
ECR only	94(45.6%)
ECR+NAC+Steroids	43(20.9%)
ECR+NAC+Steroids+Antibiotics	35(17.0%)

I.V: Intravenous; PPI: Proton Pump Inhibitor; NAC: N-Acetyl Cysteine; ECR: Extra Corporeal Removal

Table 2. Treatment for Paraquat poisoning

Assessment of outcomes in various ECR methods. *Primary treatment outcomes in ECR.* A total of 128 patients underwent ECR treatment and we observed that these patients had a higher improvement in treatment outcome than patients who did not undergo ECR therapy as depicted Table 3. We observed that survival outcome analysis between ECR group and without ECR group showed no statistically significant difference (OR: 0.711, 95% CI (0.371-1.360), p=0.336) However among the various ECR methods, highest survival rate was observed in HP (p=0.002) as shown in Table 4.

ECR	Treatment		Total	Odds ratio (95% CI)	p value
	Improved	Death			
Yes	38(29.68%)	90(70.31%)	128	0.711 (0.371-1.360)	0.336
No	18(23.07%)	60(76.92%)	78		
Total	56	150	206		

ECR: Extra Corporeal Removal, CI: Confidence Interval. p value has been calculated by Chi-square method.

Table 3. Survival outcome analysis of ECR compared to non-ECR group among the patients admitted to an Indian tertiary care teaching hospital with Paraquat poisoning between 2012 and 2019.

Outcomes	Extra Corporeal Removal Methods			
	HD	HP	HD+HP	HF
Primary outcomes				
Improved	2(7.4%)	29(43.9%)	7(21.2%)	0
Death	25(92.6%)	37(56.1%)	26(78.8%)	2(100%)
Secondary Outcomes				
Intubation	19(70.4%)	19(28.8%)	22(66.7%)	
Mean Hospitalisation days±SD	7.62±8.08	8.75±6.52	7.84±5.72	
Median (IQR) Hospitalization days	3 (2-11)	7 (3-14)	5 (4-11)	
Mean ICU days duration±SD	7.03±7.20	4.66±3.43	6.33±4.69	
Median (IQR) ICU days	3 (2-10)	4 (2-6)	5 (3-8)	
Mean Ventilator days±SD	3.70±6.33	0.63±1.61	2.42±3.17	
Median (IQR) Ventilator days	1 (0-3)	0 (0-1)	1 (0-4)	
Secondary Complications	5(18.5%)	5(7.6%)	5(15.2%)	

HD: Hemodialysis, HP: Hemoperfusion, HF: Hemofiltration, SD: Standard Deviation, IQR: Inter Quartile Range.

The primary outcomes were analyzed by using Chi-Square test among the various ECR methods and p value was found to be significant ($^{*}p=0.002$)

Table 4. Analysis of various extracorporeal removal methods with primary outcomes and secondary outcomes in patients admitted to an Indian tertiary care teaching hospital with Paraquat poisoning between 2012 and 2019

Secondary outcomes in various ECR methods. In our study population we compared the secondary outcomes with different ECR methods as shown in Table 4. Two patients were excluded who underwent HF therapy for the analysis purpose and it was found that HP was better in terms of percentage of development of intubation, mean ventilator days, mean ICU days and percentage of development of secondary complications.

*Incidence of secondary complications in various ECR methods***.** Chi-square test was conducted to find out whether there is any significant association between various ECR and secondary complications. HD, HP, HP+HD and HF groups showed statistically significant association between multiple organ dysfunction syndrome (MODS) (p=0.012), acute kidney injury (AKI) (p=0.005) and sepsis (p=0.001) respectively and not in the secondary disease groups of ARDS (p=0.375), Upper gastrointestinal bleeding (UGI) bleeding (p=0.982) and other complications (p=0.596). However, hemoperfusion (HP) showed lower incidence for MODS (12.1%), AKI (22.7%) and sepsis (12.1%) among the statistically significant ECR groups. HD showed higher incidences of MODS (40.7%), AKI (55.6%) and sepsis (29.6%) among the statistically significant ECR group as depicted in Table 5.

ARDS: Acute Respiratory Distress Syndrome, MODS: Multiple Organ Dysfunction Syndrome, AKI: Acute Kidney Injury, UGI: Upper Gastro Intestinal, HD: Hemodialysis, HP: Hemoperfusion, HF: Hemofiltration.

Table 5. Analysis of complications with various extracorporeal removal methods in patients admitted to an Indian tertiary care teaching hospital with Paraquat poisoning between 2012 and 2019.

Secondary Complications	Extra Corporeal Removal Methods				
	HD N=27	HP N=66	HP+HD N=33	HF N=2	p value
ARDS	7(25.9%)	17(25.8%)	6(18.2%)	0	0.375
MODS	11(40.7%)	8(12.1%)	10(30.3%)	0	0.012
AKI	15(55.6%)	15(22.7%)	14(42.4%)	0	0.005
Sepsis	8(29.6%)	8(12.1%)	9(27.3%)	2(100%)	0.001
UGI Bleeding	1(3.7%)	3(4.5%)	2(6.1%)	0	0.982
Other Complications	8(29.6%)	12(18.2%)	6(18.2%)	0	0.596

Discussion

Paraquat poison is one of the leading causes of fatal poisoning globally. There is an increase in the incidence of self-harm with the use of paraquat poison in the developing nations. Our study included 206 patients presented to the emergency unit with the consumption of paraquat poison.

Current study identified that majority of the poisoning were due to intentional self-harm which is in similar line with a study conducted by Mehrpour O et al [6] which had 61 (48.4%) intentional self-poisoning cases. The mean age of subjects in our study was found to be 28.14±11.35 years which was in accordance with a study by Cherukuri H et al. [7] which was 25.38 ± 9.136 years. Gender wise distribution showed male predominance 131 (63.6%) which agrees with a study conducted by Delirad et al. [8] where majority of the study population were male (n=23, 56.1%).

Among 206 included patients in this study, it was observed that psychiatric illness is one of the major risk factors for self-harm, 23 (11.2%), which can be correlated to a study by Cherukuri H et al. [7] which states that 60 of 4 (6.7%) patients had psychiatric illness and it is one of the risk factors for the intentional self-harm.

Among our study population, majority of the patients presented with vomiting 115 (55.8%), oropharyngeal burns 60 (29.1%). The similar clinical features were observed in a study conducted by Elenga et al. [9] where, all the included patients had vomited before being admitted to the hospital. However, 22 patients (32%) had epigastric pain and inflammation of the oral mucosa.

Patients in our study were given various treatments like gastric lavage, I.V. fluids, NAC and other antioxidants, immunosuppressants, proton pump inhibitors, antibiotics, ECR methods and also with combinations of the mentioned treatments. This agrees with a study by Sukumar CA et al. [10] which considers gastric lavage with activated charcoal or Fuller's earth for initial treatment, hemoperfusion is the first and the earliest modality of treatment of removal of paraquat, immunosuppressants are used to suppress acute inflammatory response leading to alveolitis and subsequently lung fibrosis and administration of antioxidants has also been tried to overcome circulatory shock due to reactive oxygen species.

Patients in our study underwent various ECR methods namely HD, HP, HP+HD and HF. We observed that patients who received HP, has shown better survival rate when compared to the other ECR methods. A

meta-analysis conducted by Holubek, W.J et al. [11] concluded that HP is the more effective method than HD for removal of paraquat toxin and decrease mortality. Moreover, another study by Yen T et al. [12] reported that early hemoperfusion have decreased mortality compared to other ECR methods.

Secondary outcomes were analysed with different ECR methods (Table 4). In our study population, only two patients underwent for HF and both cases expired, as this will affect the overall results of the study, both of these cases were excluded from the analysis. However for the other groups the values viz. hospitalisation days, ventilator days and ICU days were presented in mean±SD and median (IQR). We observed there was a variation among the mean and median values probably due to individual patient variation with respect to age, co-morbidities and pre -hospitalization during admission.

A total of 128 patients undergone ECR treatment, had positive outcome when compared to no ECR group. However, there is no statistical significance (p=0.336) with respect to ECR group to no ECR group. It has been evident that the ECR methods have decreased mortality than conservative treatment group [5].

In our study, the frequencies of development of secondary complications associated with paraquat poisoning were compared with the different ECR methods. We observed that HP showed lower incidence of AKI, MODS and sepsis among the various ECR groups which are statistically significant. According to a study conducted by Li, H. et al [5], HP group of patients have a lesser occurrence of MODS.

As of our knowledge this is the seven years long duration with good sample size retrospective study design in India to provide evidence that HP is the best suited ECR method in the comparison of other ECR method in eliminating paraquat from the body. Few limitations in the study were, since this was a retrospective study, sample size was not equally distributed in different ECR groups. Discharge against medical advice may lead to individual variability in patient outcomes.

In conclusion,among the various treatments, ECR of paraquat was found to be beneficial in terms of survival rate and among various ECR methods, HP was found to be effective in terms of mean ventilator days, and mean ICU days and reduced percentage of development of secondary complications, mainly includes MODS, AKI and sepsis.

Methods

Ethical consideration. The study was approved by Kasturba Medical College and Hospital Institutional Ethics Committee (IEC Project No: 546/2019).

Ethical approval was obtained from Kasturba Medical College and Hospital Institutional Ethics Committee, and procedures were performed in accordance with the Declaration of Helsinki and Good Clinical Practice. The need of informed consent was waived by approving ethical committee/institutional review board.

Study Setting and Participants. A total of 303 patients irrespective of age and gender were enrolled in the study. Patients were included only if it is diagnosed as paraquat poisoning during admission in the emergency department. Patients with glyphosate, fungicide and other herbicide poisoning were excluded from the study. Based on inclusion and exclusion criteria, 206 patients were enrolled and data was retrieved from the medical record. Overview of the study is depicted in Figure 1.

Data collection. Data of patients identified with paraquat poisoning along with other herbicide and fungicide poisoning (ICD coding T60.3X1D) was collected retrospectively from medical records department (MRD). All the patients diagnosed with paraquat poisoning were enrolled in this study. Details of the patients including demographics, severity of poisoning, dose of poison, biochemical parameters and treatment such as antioxidants, immunosuppressants and ECR methods were recorded in an appropriately designed case report form (CRF). In our study, outcome measures are categorized into primary outcomes (improved and unimproved) and secondary outcomes (days of hospitalization, days in ICU, days on ventilator and development of secondary complications).

Outcome Measurement. Outcome measures were categorized into primary outcomes by the analysis of clinical improvement or clinical unimprovement. Clinical improvement is the complete resolution of all signs and symptoms of poisoning, improvement of vital signs and abnormal biochemical values. Clinical unimprovement includes patients who died (no improvement in signs and symptoms and discharged against medical advice) and secondary outcomes (days of hospitalization, days in ICU, ventilator days and development of secondary complications).

Statistical Analysis. All the data collected were analyzed using Statistical Package for the Social Sciences (SPSS) 20.0 package. Continuous data was analyzed using mean±SD and categorical variables were analyzed using frequency. Cross-tabulation by Chi-square method was used to determine the significant association between categorical variables.

Data availability. The data that support the findings of this study are available from the corresponding author on request.

Declarations

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Balaji Sridhar, Jemima Pappu Raj, Athira Balakrishnan and Girish Thunga. Conceptualization and methodology were performed by Girish Thunga, Shivashankar K N. The first draft of the manuscript was written by Balaji Sridhar and Jemima Pappu Raj. Review and editing were performed by Vijayanaryana Kunhikatta and Pooja Gopal Poojari and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical declarations

Competing interest

The authors have no conflict of interest to disclose.

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Figures

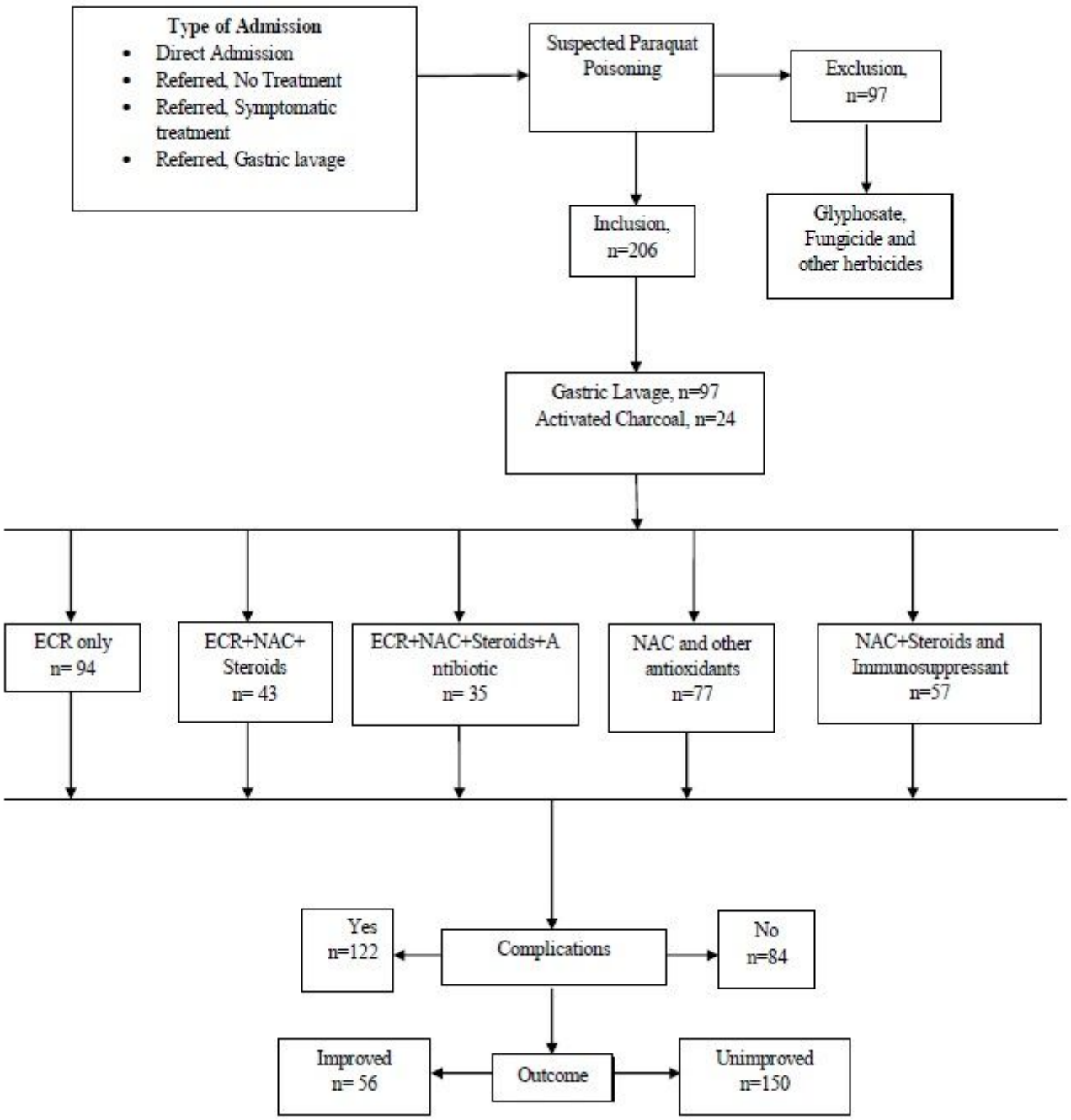

Figure 1