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Original Article

Internal Medicine Section

The Corticosteroids in Paraquat Poisoning-Are They the Sole Life-saving Drugs?: A Prospective Cohort Study

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ABSTRACT

Introduction: Paraquat poisoning has the highest mortality rate, as high as, 50%-90% due to multiorgan failure, inspite of early interventions by symptomatic medications in the best intensive care settings. The high degree of acute inflammation was found in the subjects of paraquat poisoning with multiorgan failure. There are no specific antidotes at present for the paraquat poison.

Aim: To know the role of corticosteroid as a life-saving drug in paraquat poisoning.

Materials and Methods: This prospective cohort study was conducted in the Department of Internal Medicine at KR Hospital, Mysuru, Karnataka, India. The duration of the study was eight months, from August 2022 to March 2023. A total of 108 subjects suffering from paraquat poisoning and were divided into two arms, arm one constitutes 70 (64.8%) subjects, they were given 1 gm of methylprednisolone, intravenously for five days with haemoperfusion. The arm two constitutes 38 (35.2%) subjects, they were treated with symptomatic drugs with haemoperfusion. Both the groups were followed-up during the hospital stay, to look for the outcome. The Chi-square test was applied to assess the association between two variables. The data was analysed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Chicago).

Results: The present study was done on 108 subjects, 43 (39.81%) were females and 65 (60.18%) were males. The majority of subjects showed high level of acute inflammatory mediators with multiorgan dysfunction. The subjects on corticosteroids (i.v. methylprednisolone) with haemoperfusion showed low mortality 12 (17.14%) and high survival rate 58 (82.85%) (p-value=0.001) as compared to the subjects on symptomatic treatment with haemoperfusion, with mortality of 36 (94.73%) (p-value=0.01).

Conclusion: The early administration of high doses of corticosteroids in subjects with paraquat poisoning had been shown to provide tangible and measurable mortality benefits as compared to the symptomatic medications.

Keywords: Haemoperfusion, Inflammation, Methylprednisalone, Mortality

INTRODUCTION

Paraquat ingestion is a major cause of fatal poisoning in Southeast Asia as, it was widely used as an herbicide by majority of farmers [1]. The reason for the consumption of paraquat among the youth may be due to its easy availability and wide usage as an herbicide [1]. Paraquat poisoning has the highest mortality rate, as high as, 50%-90% due to multiorgan failure, suggesting that, there may be a significant associated immunological hyperactivity [1,2]. The commonest method of poisoning with paraquat was an oral intake [3]. Mortality rate of paraquat poisoning was directly related to plasma and urine levels of paraquat [4]. Several mechanisms have been reported to be involved in the tissue injury caused by paraquat poisoning, such as, redox reaction by reactive oxygen species and lipid peroxidation of cellular membranes [5]. The patients suffering from parquet poisoning, exhibited a severe level of acute inflammation in their bodies, resulting in substantial tissue damage and ultimately leading to multiorgan failure [5,6]. At present, there is no specific antidote for the treatment of paraquat poisoning [2,7]. In subjects with severe poisoning, it is difficult to have positive prognosis, even with various available non specific and symptomatic treatment methods [8]. Early prediction of the severity of acute paraquat poisoning was of great help in order to have a reasonable and appropriate treatment [8]. In the initial stages of paraquat poisoning, haemoperfusion was the preferred mode of therapy in treating these subjects as, it was primarily excreted by the kidneys [2,9]. Some studies have found that, the haemoperfusion was not useful for the reason that, the potentially lethal concentration of paraquat might get accumulated in highly vascular tissues of the vital organs and pneumocytes, before the initiation of haemoperfusion [2,10].

The peak time of plasma concentration of paraquat after consumption was one to three hours, that of lung tissue level was within four to five hours and nearly 90% of the paraquat disappears from the blood within five to six hours of ingestion. Hence, the subjects who received early haemoperfusion within six hours of consumption were likely to be benefited, due to significant removal of the amount of paraquat from the blood [2,8,10] and this indirectly reduced the amount of paraquat getting accumulated in the lung tissue also, thereby, improving the outcome [2]. Several diagnostic tests were used to confirm the paraquat consumption, like estimation of serum and urine levels of paraquat. But, these tests might not add any extra benefits due to the rapidity at which the damage occurs in paraqaut poisoning [11]. However, these prognostic markers cannot be applied widely in all hospitals in the developing countries like India, due to the higher technical requirement of assay, complicated calculation, financial constraints and its not feasible to be done in so many laboratories for unknown reasons. The high degree of organs injury with multiorgan failure with high degree of acute inflammation is found in paraquat consumption subjects [12]. As per the author's knowledge, there were limited studies to prove the benefits of high dose of corticosteroids in paraquat poison subjects. In view of no specific antidotes at present and also, presentation with high degree of acute inflammation with multiorgan failure and high rate of death. The present study was undertaken to find the significant role of high dose of corticosteroids in preventing morbidity and mortality in paraquat poisoning subjects.

MATERIALS AND METHODS

A prospective cohort study was conducted in the Department of Internal Medicine at KR Hospital, Mysuru, Karnataka, India.

The duration of the study was eight months, from August 2022 to March 2023. The present study was started after getting the Institutional Ethical Committee (IEC) approval from Mysore Medical college and Research Institute with the letter number, (EC REG:ECR/134/Inst/KA/2013/RR-19) and after getting the valid informed consent from subjects.

Inclusion criteria: All subjects with paraquat consumption with age >18 years were included in the study.

Exclusion criteria: Subjects with pre-existing renal dysfunction, liver dysfunction, any type of cardiac illness, connective tissue diseases, autoimmune diseases, on any chronic drug intake including antimetabolites and steroids, immunocompromised status and any type of malignancy were excluded from the study.

Sample size calculation:

$$N=Z^2PQ/d^2$$

Z=Two standarad deviation with 95% confidence interval (1.96*1.96)

P=Prevalence rate of acute poisoning in emergency department is 1.7% [13]

Q=1-P

d^2=Precision value of 0.05

Study Procedure

The complete history of poison consumption and clinical examination was done for all the subjects. The blood sample was collected from all the poison consumed subjects on the day one, day five and day 10 of consumption and the following investigations such as Complete Blood Count (CBC), Random Blood Sugar (RBS), Renal Function Test (RFT), Liver Function Test (LFT), Arterial Blood Gas (ABG), High sensitivity C-reactive protein (hsCRP) (normal level <1 mg/L), Lactate Lehydrogenase (LDH) (normal level 140 to 280 IU/L) [14-16] and serum ferritin (normal level 20-200 µg/L) levels were measured. Other tests such as, Electrocardiogram (ECG) ultrasound scan of abdomen and chest X-ray were done, wherever, it was necessary. The subjects were divided into two arms, the arm one constitutes 70 subjects with their consent for the usage of corticosteroids, all of them were given Methylprednisolone 1 gm once a day for five days with haemoperfusion [2] and the arm two constitutes of 38 subjects, who have not given consent for corticosteroids, all of them were given symptomatic treatment, such as vitamin E, N acetyl cysteine, vitamin C, opioid analgesics with haemoperfusion [2,8]. The haemoperfusion was initiated within six hours of paraquat consumption in most of the patients [2]. The subjects were followed-up for the whole duration of hospital stay and the outcomes were recorded in the pretested proforma. The data was tabulated and analysed by using the appropriate statistical method.

Proforma for paraquat consumption study:	
Date and time:	
Name:	
Occupation:	
Age:	
Address:	
Gender:	
Amount of paraquat consumed:	
Presenting complaints:	
Past and social history:	
General physical examination findings:	
Systemic examination:	
Investigations:	
Treatment offered:	
Outcome:	
Follow-up	

STATISTICAL ANALYSIS

In the present study, the data was analysed using SPSS version 25.0 (IBM Chicago). The descriptive statistics with mean and standard deviation was used for the analysis of age, gender, clinical features and all the investigational values. The Analysis of Variance (ANOVA) and multivariate regression analysis tests were used to look for the association between multiple variables. The Chi-square test was used to assess the association between two variables. The (p-value <0.05) was taken as statistically significant.

RESULTS

The present study was done on 108 subjects of paraquat poisoning, constitutes about 70 (64.8%) on corticosteroids and 38 (35.2%) on symptomatic treatment. The subjects age between 18 to 29 years, were reported more in number with paraquat consumption than, the other age group subjects. In the present study, 43 (39.81%) subjects were females, whereas, 65 (60.18%) were males. All subjects with paraquat poisoning had oral mucosal burns. All subjects were having elevated serum acute inflammatory mediators even on day 10 of paraquat poison consumption [Table/Fig-1].

Demographic parameters		**n (%)**
Age (in years)	>60	8 (7.4)
	40-59	23 (21.29)
	30-39	29 (26.85)
	18-29	48 (44.44)
Gender	Female	43 (39.81)
	Male	65 (60.18)
Dose of paraquat consumed	<20 mL	68 (62.96)
	>20 mL	40 (37.03)
Clinical features	**Days**	**n (%)**
Oralmucosal burns	1, 5 and 10	108 (100)
Renal failure	1, 5 and 10	106 (98.14)
		106 (98.14)
		106 (98.14)
Liver dysfunction	1, 5 and 10	05 (4.63)
		86 (79.62)
		88 (81.48)
Lung dysfunction	1, 5 and 10	05 (4.6)
		12 (11.11)
		12 (11.11)
Cardiovascular dysfunction	1, 5 and 10	68 (62.96)
		21 (19.44)
		04 (3.7)
Neurological dysfunction	1, 5 and 10	02 (1.85)
		02 (1.85)
		02 (1.85)
Laboratory parameters	**Days (1, 5 and 10)**	**n (%)**
hs CRP level (mg/L) mean±SD	24.06±4.51	108 (100)
	18.70±4.06	108 (100)
	19.53±5.93	108 (100)
Serum ferritin level (µg/L) mean±SD	680.48±56.89	108 (100)
	631.94±132.97	108 (100)
	698.66±182.6	108 (100)
LDH level (IU/L)mean±SD	418.68±63.5	108 (100)
	663.49±131.0	108 (100)
	88.05±171.51	108 (100)

[Table/Fig-1]: Showing demographic, clinical and laboratory features N=108.

The acute inflammatory markers were elevated consistently in most of the subjects with vital organs dysfunction [Table/Fig-2].

The serum hs-CRP (p-value=0.01) ferritin (p-value=0.04), LDH (p-value=0.05) levels were significantly decreased on day 5 and day 10 of the treatment in arm one subjects than in arm two [Table/Fig-3].

Major clinical features	Number of subjects with elevated inflammatory markers n (%)			p-value
	hs-CRP level of 20.76±4.83 (mean±SD in mg/L)	Serum ferritin level of 670.36±124.15 (mean±SD in µg/L)	Serum LDH level of 590.07±122.0 (mean±SD in units/L)	
Oral mucosal burns	108 (100)	108 (100)	108 (100)	0.001
Renal failure	106 (98.14)	90 (83.33)	98 (90.74)	0.05
Liver dysfunction	88 (81.48)	84 (77.77)	84 (77.77)	0.05
Lung injury	12 (11.11)	12 (11.11)	1211.11)	0.04
Cardiovascular abnormality (hypotension and myocarditis)	68 (62.96)	59 (54.62)	65 (60.18)	0.05
Neurological abnormality (peripheral neuritis)	02 (1.85)	02 (1.85)	02 (1.85)	0.04

[Table/Fig-2]: Shows association between major clinical features and inflammatory markers.
Multivariate regression analysis was the statistical method applied N=108

Parameters	Subjects on medications							
	Methylprednisolone and haemoperfusion, n=70			p-value	Symptomatic drugs and haemoperfusion, n=38			p-value
Level of inflammatory mediators	Day 1	Day 5	Day 10		Day 1	Day 5	Day 10	
hs-CRP level in mg/L (mean±SD)	24.06±4.51	9.41±2.45	4.5±1.4	0.01	24.06±4.51	28.01±5.68	34.56±10.46	0.01
Ferritin level in µg/L-mean±SD	680.48±56.89	410.23±78.68	331.56±78.56	0.04	680.48±56.89	853.65±186.46	1065.76±286.64	0.05
LDH level in IU/L mean±SD	418.68±63.5	562.34±105.56	341.54±86.46	0.05	418.68±63.5	764.65±156.45	1034.65±256.56	0.05

[Table/Fig-3]: Showing association between serum acute inflammatory markers and medications of subjects.
The ANOVA was the statistical test applied N=108

The subjects on methylprednisolone group had less mortality (17.14%) and high survival rate (82.85%) (p-value=0.001) as compared to the subjects in arm two with, the mortality (94.73%) (p-value=0.01) [Table/Fig-4].

Subjects outcome	Subjects on medications- n (%)		p-value
	On methylprednisolone and haemoperfusion n=70 (%)	On symptomatic treatment and haemoperfusion n=38 (%)	
Survived	58 (82.85)	02 (5.26)	0.001
Died	12 (17.14)	36 (94.73)	0.01

[Table/Fig-4]: Shows association between subjects on medications and outcome.
Chi-square test was applied N=108

DISCUSSION

The present study was conducted to find the mortality benefits of high dose of corticosteroids with haemoperfusion in subjects of paraquat poisoning as compared to the subjects on symptomatic treatment with haemoperfusion. In the present study, the paraquat consumption was more commonly found in the age group between 18 to 29 years than in other age group and it was more common in males 65 (60.18%) than female subjects. As compared, with the study by Rao R et al., where, the mean age of the study subjects was 26.97 years, where 66 (65.3%) were males [2]. In the present study, more number of subjects 68 (62.6%) consumed less than 20 mL of paraquat substance. The Mohammad D et al., study says that, the fatal dose of paraquat poison was 30 mL in adult population and it was enough to cause severe toxicity and damage to all vital organs [17]. Most of the subjects of paraquat consumption had oral mucosal burns in the present study. The significant number of subjects had renal and liver dysfunction, which persisted throughout the hospital stay duration. As per the study by Roberts Darren M the most common and significant injury happens to mucosa of oral cavity, mucosa of gastrointestinal tract in the early period and subsequently the vital organs like kidney, liver and lungs would get affected in paraquat poisoning [18]. In majority of subjects irrespective of the dose of paraquat consumption and early interventions, the renal, liver and lung injury happens and it may lead in to early death [18]. In the present study, more number of subjects with paraquat consumption had significantly elevated the levels of acute inflammatory mediators, such as hs-CRP, LDH and serum ferritin. The Ju-Shao Y et al., study shows that, the high degree of disproportionate acute inflammation with high level of cytokines were found in the blood samples of subjects with paraquat poisoning in the first 24 hours [19]. This shows that, the high degree of acute inflammation due to paraquat induced injury could be the perpetuating causes of progressive multiorgan failure and detrimental outcome of paraquat poisoning [20]. In the present study, subjects on corticosteroids (methylprednisalone) with haemoperfusion had sequentially reduced levels of acute inflammatory mediators than in the subjects on symptomatic treatment with haemoperfusion. Subsequently, the subjects on methylprednisolone with haemoperfusion had reduced mortality (17.14%) (p-value=0.01) and increased survival rate (82.85%) (p-value=0.001) than the subjects on symptomatic treatment with haemoperfusion [Table/Fig-4]. This shows that, in the absence of specific antidotes for the management of paraquat poisoning, the methylprednisolone (corticosteroids) comes out as a life-saving drug. The study by Lin G et al., says that, haemoperfusion with in first two to six hours of paraquat consumption could prevent severity of organs injury and death [21]. A study by Li LR et al., says that, the early use of corticosteroids and immunosuppresants have got significant role in preventing death in paraquat poisoned subjects [22]. This again confirms that, the paraquat poison induced organs injury and the acute hyper inflammatory response with multiorgan dysfunction could be the significant reason for the morbidity and mortality [23]. Once again the present study links the pathophysiology of paraqaut poisoning into disproportionate acute inflammation and immunological response to toxic end products of paraquat.

Limitation(s)

The study sample size was limited and suggested to confirm the benefits of corticosteroids in paraquat poisoning by studying on larger sample size. The blood and urine paraquat level was not measured, because of feasibility constraints.

CONCLUSION(S)

There is a proven benefit of high dose of corticosteroids in preventing mortality in paraquat poisoning in the era of no specific antidotes. The present study again confirms that, the disproportionate high degree of acute inflammation could be the probable cause of morbidity and mortality in paraquat poisoning and also, endorses the high dose of corticosteroids in preventing complications and death in paraquat poisoning subjects.

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