ORIGINAL ARTICLE

Paraquat Poisoning: Experience in Hospital Taiping (Year 2008 - October 2011)

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SUMMARY

Introduction: Paraquat is a quaternary nitrogen herbicide which is highly toxic to human. Death is usually from respiratory failure and may occur within days up to a month after exposure. It is easily available and commonly abused to commit suicide.

Methodology: This is a retrospective study describing the demographic characteristics, clinical features and outcomes of paraquat poisoning cases admitted to Hospital Taiping from 1st January 2008 to 30th October 2011. Medical records of 79 patients were reviewed.

Result: Majority were of the Indian ethnicity (72.2%) followed by Chinese (13.9%) and Malay (10.1%). Majority was male (73.4%) and between 20 to 29 years old (34.2%). The median age of the patients was 30 years old. The mean length of stay was 6.2 days. Most exposures were intentional (69.6%) and presented to the hospital early at less than 6 hours after exposure (72.2%). Patients with positive urine paraquat result had significantly higher mortality rate compared to patients with negative results (47.4% vs 15.2% respectively). We found that neither hemofiltration nor immunosuppressive therapies help to improve survival.

Conclusion: The non-survivor characteristics of patients with paraquat poisoning are intentional exposure, delay from exposure to hospital admission, urine paraquat positivity and manifestation of respiratory failure. The demographic characteristics, reasons for exposure and mortality rate are similar to previous reports. Urine paraquat may be used to assess severity of the exposure as well as prognosis. Hemofiltration and immunosuppression therapy do not improve patients' survival and paraquat remains a lethal killer.

KEY WORDS:
Paraquat poisoning; herbicide; suicide; mortality

INTRODUCTION

Paraquat is a quarternary nitrogen herbicide that is sprayed on weeds and other vegetations before crops planting. It is a fast-acting and non-selective compound which destroys tissues of green plants on contact and by translocation within the plant. Paraquat exerts its herbicidal activity by inhibiting reduction of NADP to NADPH during photosynthesis. This disruption leads to the formation of superoxide anion, singlet oxygen, as well as hydroxyl and peroxyl radicals. These reactive oxygen species (ROS) interact with the unsaturated lipids of membranes, resulting in the destruction of plant organelles, inevitably leading to cell death [1].

Paraquat has been demonstrated to be a highly toxic compound for human and animal. Many cases of acute poisoning and death have been reported over the past few decades. It is acutely toxic and enters the body mainly by swallowing, dermal exposure or inhalation. As little as a teaspoon of concentrated paraquat can result in death. It is usually due to respiratory failure and may occur within few days or some time as long as a month after the exposure. Besides the lung, paraquat also damages the heart, kidneys, adrenal glands, central nervous system, liver, muscles and spleen causing multiple organ failure [2-5]. Clinical reports associated paraquat poisoning with acute lung injury, pulmonary hypertension, leucocytosis and metabolic acidosis, enlarged heart [6], acute kidney injury [7], generalized edema and increased level of amylase, glucose and creatinine [8]. Up till now, there is no antidote known to be effective.

Paraquat is one of the most common and lethal herbicide to cause deaths from suicide. The mortality rate ranged from 60 to 70% [9] - much higher than any other agents. The use of paraquat to commit suicide is also reported worldwide. In developing countries such as Sri Lanka, intentional self poisoning is often a result of impulsive behavior rather than long-standing psychiatric illness. Most of the intentional self poisoning occurs via ingestion with sudden grief and anger as the common triggers [10]. Manuel et al reported that in Sri Lanka, there was about 300-400 self-poisonings with pesticides per 100,000 populations each year [11]. Hutchingson et al also reported that from the year 1986 to 1990, 63% of all suicide deaths in Trinidad and Tobago were due to paraquat poisoning [12].

If the general perception is that the use of paraquat for deliberate self harm or suicides is mainly a problem in developing countries, Casey et al proved otherwise when they reported that between the year 1945 and 1989, paraquat was responsible for 56% of all pesticide deaths in England and Wales [13] while more recently Bronstein et al reported that in America, it was the cause for more deaths than any other pesticide in 2008 [14].

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In Malaysia, numerous cases of intentional self poisoning with paraquat have been reported. However, there is not many published literature on studies done locally. A study on paraquat poisoning in the state of Perak in 1984 [15] found that 73.4% of the cases were suicide attempts. The study also reported mortality rate of 64.9%. During the period of 1986-1996, paraquat was reported as the cause of nearly 700 cases of poisoning in Malaysia. Of these, 73% are due to suicide while the remainders were accidental and occupational exposures [16]. From year 2005 to 2010, there were 14 deaths due to paraquat poisoning were recorded in Tanjong Karang Hospital, a 114-bedded district hospital in rural Selangor [17]. However, the reason for the poisonings was not reported.

According to National Poison Centre, the number of paraquat poisoning cases has been rising in recent years. The sale of paraquat was banned from the year 2002 to 2006. Since 2006 when the ban was lifted, the number of paraquat poisoning cases reported has more than doubled up till the year 2008 where there was 7 times the number of cases reported compared to the years when it was banned [18].

Paraquat poisoning remains a public health concern in Malaysia due to its high mortality and significant morbidity. However, there is limited publication of local data in regards to paraquat poisoning, particularly since the lifting of the ban in 2006. This study aims to describe the demographic characteristics, clinical features and outcomes of paraquat poisoning cases recorded in Hospital Taiping from 1st January 2008 to 30th October 2011.

MATERIALS AND METHODS

This is a retrospective study of patients admitted to the medical wards of Hospital Taiping for alleged paraquat poisoning. No personal identification data were recorded and all information obtained from the medical records was kept confidential. This study was approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH) with waiver from full board review.

Setting

Taiping Hospital is the second largest public hospital in the state of Perak. The medical unit of Taiping Hospital has a total of 176 beds. As the referral centre for Northern Perak, Taiping Hospital caters to a catchment area of 504,327 people from the districts of Larut, Matang, Selama, Kuala Kangsar and Kerian [19].

Subjects

The study included patients above the age of 12 who were presented to the Emergency Department with paraquat poisoning during the study period. This includes patients who self-admitted or with witness account of paraquat exposure (inhalational, mucosal or skin contact, ingestion).

Data collection

Data was obtained manually from the patient's medical records. The information recorded is age, gender, time from ingestion to hospital admission, amount ingested, symptoms, length of hospital stay (LOS), treatment received and outcome.

Statistical analysis

Descriptive statistics were used to summarise the demographic characteristics, clinical features and outcomes of the cases. The variables were also compared between survivors and non-survivors. The results were presented as mean ± standard deviation and percentage, where appropriate. The t-test was used to investigate the differences of continuous variables between survivors and non-survivors. The relationships between categorical variables and the outcomes were evaluated using chi square test where appropriate. The data was analysed using the IBM SPSS Statistics version 20. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

The medical records of 79 patients were reviewed in this study. Majority were of the Indian ethnicity (n=57, 72.2%) followed by Chinese (n=11, 13.9%) and Malay (n=8, 10.1%). Male made up the majority with 73.4% (n=58). The mean age of the patients was 36 years (SD=17.1). The mean length of stay was 6.2 days (SD=4.1). The mortality rate in this study was 31.6% (n=25). The outcome of 4 patients were not known as they requested discharge at own risk (AOR) and were lost to follow up.

Majority of the patients reported intentional exposure (n=50, 69.6%) with another 26.6% were accidental (n=21). The rest of the cases were occupational exposure (n=3, 3.8%). Most of the patients presented to the hospital early at less than 6 hours after exposure (n=57, 72.2%). Another 11.4% presented between 6 to 24 hours and the remaining 13.9% presented after 24 hours (n=9 and n=11 respectively).

71 patients (89.9%) had their urine paraquat result documented in their records. Of these patients, 38 (53.5%) had positive results. For the group of patients presented after 24 hours of exposure, the result for urine paraquat measurement may not be relevant because paraquat is rapidly absorbed and excreted in urine within 12-24 hours.

Table I: Demographic characteristics of the patients

	Number of patients (%) N = 79
Age (years)	
< 20	12 (15.2)
20 – 29	27 (34.2)
30 – 39	12 (15.2)
40 – 49	9 (11.4)
50 – 59	9 (11.4)
> 59	10 (12.6)
mean ± SD	36.04 ± 17.05
median	30
Gender	
Male	58 (73.4)
Ethnicity	
Malay	8 (10.1)
Chinese	11 (13.9)
Indian	57 (72.2)
Others	3 (3.8)
Year of admission	
2008	21 (26.6)
2009	19 (24.1)
2010	23 (29.1)
2011 (till Oct)	16 (20.3)

Table II: Clinical characteristics and outcome of the patients

	Number of patients (%)		p value
	Survivor	Non-survivor	
Year of admission			
2008	14 (66.67)	7 (33.3)	0.320
2009	12 (63.2)	7 (36.8)	
2010	19 (82.6)	4 (17.4)	
2011 (till Oct)	9 (10.9)	7 (43.8)	
Total	54 (68.4)	25 (31.6)	
Reason for exposure (n=78)			
Intentional	35 (68.4)	19 (35.2)	0 (0.0)
Accidental	16 (76.2)	5 (23.8)	
Occupational	3 (100.0)	0 (0.0)	
Time from exposure to admission (n=77)			
< 6 hours	42 (73.7)	15 (26.3)	0.178
6-24 hours	6 (66.7)	3 (33.3)	
>24 hours	5 (45.5)	6 (54.5)	
Urine paraquat test (n=71)			
Positive	20 (52.6)	18 (47.4)	0.004
Negative	28 (84.8)	5 (15.2)	
Respiratory failure (n=79)			
Yes	2 (8.7)	21 (91.3)	<0.001
No	52 (92.9)	4 (7.1)	
Hepatitis (n=73)			
Yes	2 (22.2)	7 (77.8)	0.001
No	48 (75.0)	16 (25.0)	
Shock (n=71)			
Yes	0 (0)	8 (100.0)	<0.001
No	49 (77.8)	14 (22.2)	
Serum Creatinine, mean ± SD (mol/L)	107.3 ±130.8	293.4 ± 254.2	<0.001
Length of stay, mean ± SD (days)	3.46 ± 3.03	5.38 ± 10.3	0.003

Table III: Treatment characteristics and outcomes of the patients

	Number of patients (%)		p value
	Survivor	Non-survivor	
Haemodialysis / haemoperfusion (n=79)			
Yes	11 (45.8)	13 (54.2)	0.004
No	43 (78.2)	12 (21.8)	
Immunosuppression (n=79)			
Yes	14 (56.0)	11 (44.0)	0.108
No	40 (74.1)	14 (25.9)	
Charcoal (n=78)			
Yes	41 (68.3)	19 (31.7)	0.754
No	13 (72.2)	5 (27.8)	
Fueller's Earth (n=78)			
Yes	30 (62.5)	18 (37.5)	0.103
No	24 (80.0)	6 (20.0)	

Table IV: Previous studies of immunosuppressive therapy in paraquat poisoning

Study	Immunosuppresive therapy	Mortality in experimental group, n/N (%)	Mortality in control group, n/N (%)
Addo (1984) - Trinidad	Dexamethasone and cyclophosphamide	5/20 (25)	Not available
Addo (1986) - Trinidad	Dexamethasone and cyclophosphamide	20/72 (28)	42/61 (68)*
Perriens (1989) - Suriname	Dexamethasone and cyclophosphamide	20/33 (61)	9/14 (64)*
Lin (1996) - Taiwan	Methylprednisolone and cyclophosphamide	17/29 (59)	23/28 (82)*
Viera (1997) - Brazil	Dexamethasone and cyclophosphamide	7/29 (28)	10/10 (100)*
Lin (1999) - Taiwan	Methylprednisolone, dexamethasone and cyclophosphamide	38/56 (68)	53/65 (82)**

Note. Adapted from "Prospects for treatment of paraquat-induced lung fibrosis with immunosuppressive drugs and the need for better prediction of outcome: a systematic review," by Eddleston M, Wilks MF and Buckley NA, 2003, Q J Med, 96(11), p. 812. Copyright 2003 by Association of Physicians.

**historical control*

*** randomized controlled trial*

In this study, we found that the survival rate for patients who had haemofiltration was 45.8% (n = 11), which is lower than patients who did not had haemofiltration (n = 43, 78.2%). The survival rate for patients who were given immunosuppression therapy were also lower at 56% (n = 14) compared patients who did not receive any immunosuppression therapy (n = 40, 74.1%).

DISCUSSION

As evident from our literature search, this is the first retrospective study on paraquat poisoning done by a local public hospital since the ban on paraquat sale was lifted in 2006. From the cases reviewed, we find that paraquat poisoning affects all ethnicity. However there is preponderance among the Indian population as indicated by higher proportion of cases which is not representative of the ethnic distribution of this area. The percentage of Indians was estimated to be 12.9% of the population in the catchment area [19] compared to case prevalence of 72.2%. Similar trend was also reported by Wong in 1984 where 81.9% of the poisoning cases reported in the state were Indians [15]. Although the proportion is lower compared to data from 1984, this study suggests that in Perak, the Indian community is still more affected than the others. Further study is needed to investigate the factors that may be associated with this pattern such as availability of the poison as well as psychosocial and cultural influence.

Many of the patients were from the age group of 20 to 29 years old (34%) with median age of 30 years. These are the productive age group in the population. Their loss can be devastating to the family as well as the society. More in-depth study is necessary to look into the reasons for this observation.

In our cohort of patients, majority of the exposures were intentional, mainly from deliberate self harm. Previous study in the state by Wong (1984) also found that suicide accounted for 73.4% of the cases [15]. Similarly, in a study conducted by National Poison Centre, suicide attempts were the most common circumstances of exposure with percentage as high as 73.8% [18]. This shows that over the last few decades, suicide remains the leading cause for paraquat poisoning and the lifting of its sales ban is not addressing the issue but facilitating it.

Even though the majority of paraquat poisoning in Taiping are intentional exposures, we must not neglect the other 26.6% of the cases which are accidental exposures. These exposures may be prevented if paraquat was not easily available as pesticides. Among the accidental exposures, unfortunately, 5 deaths were reported. Upon investigation, one of these patients had accidentally ingested the paraquat which was kept in a water bottle while under alcohol intoxication. The patient was not likely able to recognize the mistakes as his conscious mind was under the influence of alcohol.

There was also no statistical significance between timing of exposure to presentation and mortality (p = 0.178). This is likely because once ingested, it is rapidly absorbed and distributed to lung, liver, kidney and muscle where it causes damage as described above [20]. Although the difference was not statistically significant, the proportion of patients who were admitted within 6 hours of exposure and survived was higher than patients who were admitted after 6 hours (73.7% compared to 55.0%). This suggests that there may be potential benefit for patients who were treated earlier to have better outcome.

The severity and outcome of paraquat poisoning is determined primarily by the amount ingested. In most cases, it is difficult to determine accurately the exact amount ingested. In this case, measurement of paraquat level in the plasma would be helpful. However, plasma measurement of paraquat is not routinely done in Taiping Hospital and urine paraquat test was done as the alternative. It is a semi-quantitative test and has a good correlation between concentration of paraquat and intensity of the blue color formed [21]. The darker the color, the worse is the patient's prognosis. We found that of the 89.9 % of urine paraquat result that was known (n=71), 53.5% was urine paraquat positive (n=38). There is statistically significant difference in regards to urine positivity with mortality. Mortality rate for patients who had positive results in the urine paraquat test was higher at 47.4% (n=18) compared to 15.2% (n=5) in patients with negative results (p = 0.004). Therefore, in facilities without plasma paraquat measurement, urine paraquat testing may be the only option available to assess severity of exposure as well as prognosis.

To date, there is no specific and effective antidote for paraquat poisoning. Management of paraquat poisoning is mainly supportive at best. The attempts to reduce absorption are by gastric lavage, administration of Fueller's earth and skin decontamination. Subsequent management in the wards or intensive care unit would be more specific to increase elimination of the paraquat by hemofiltration (hemodialysis or hemoperfusion), and modification of tissue toxicities with immunosuppressive agents. However, we found that neither hemofiltration nor immunosuppressive therapies help to improve survival. It also has to be noted that both hemofiltration and immunosuppressive agents are costly treatments that can have significant financial impact, especially to resource-limited hospitals. With mortality rate of 54.2% and 44.0% despite hemofiltration and immunosuppression therapy respectively, paraquat remains a potent killer. The efficacy of these treatments is still debatable and may cause unnecessary drain of hospital resources.

There was heterogeneity as reported in a systematic review in regards to the use of immunosuppressive agents [22]. The mortality rate with immunosuppressive therapy ranged from 25% to 68%. However, the mortality in the control group who did not receive immunosuppressive treatment was definitely higher between 63% and 100%. In our study, the mortality rate was lower compared to previous reports probably because in some of the cases of alleged poisoning, the urine paraquat was reported negative, thus actual poisoning cannot be proven. Besides that, the severities of the exposures were not determined. Another possible reason might be

variation in the concentration of the paraquat marketed in the countries. Further study is needed to investigate specifically the effects of different paraquat concentration to mortality rate.

We identified few limitations from this study. The end-point for this study was determined when the patient was discharged from the hospital. There was no follow-up of the patients to assess the long term effect of paraquat poisoning such as development of lung fibrosis, readmission, morbidity and mortality. Despite a three-year retrospective review, the sample size is still small and lack power to conduct conclusive statistical analysis. We also cannot determine the extent of exposure and the amount ingested. As plasma paraquat measurement is not available, only urine paraquat was measured as the surrogate indicator to confirm and assess severity of exposure.

CONCLUSION

The non-survivor characteristics of patients with paraquat poisoning are intentional exposure, delay from exposure to hospital admission, urine paraquat positivity and manifestation of respiratory failure. The demographic characteristics as well as reasons for exposure and mortality rate are similar to previous reports in the country. Urine paraquat may be the alternative to plasma paraquat to assess severity of the exposure as well as prognosis. Hemofiltration and immunosuppression therapy improves patients' survival as compared to other studies and historical data, but paraquat remains a lethal killer.

RECOMMENDATION

Paraquat poisoning is preventable through primary prevention by banning its usage in Malaysia. Relevant authority should look into alternative methods or less lethal compounds as herbicide. The burden of paraquat exposure, both intentional and accidental, is an unnecessary drain of our limited healthcare resources as the management of paraquat poisoning is at best supportive in nature as there is no known antidote. The high mortality associated with paraquat poisoning has also resulted in loss of productive group in our country. If the use of paraquat can be banned in other countries, the authors are of the opinion that similar measures can be taken in Malaysia.

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