ORIGINAL ARTICLE

Paraphenylene Diamine Poisoning & Its Laboratory Profile: in Nawabshah, Pakistan. A Descriptive Study

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ABSTRACT

Objective: This study aims to analyze the laboratory findings and the extent of damage to various tissues following the paraphenylene diamine (PPD) intoxication in Nawabshah, Pakistan.

Study Design: Observational, descriptive study.

Place & Duration: Department of Medicine and Intensive Care Unit (ICU), Department of Anesthesiology, Peoples University of Medical and Health Sciences Nawabshah, Pakistan during October 2013 to October 2014.

Material & Methods: During October 2013 to October 2014, 178 consecutive patients were admitted to the Intensive Care Unit through Department of Medicine with history of hair dye poisoning and were included in the study. Demographic features, laboratory profile and outcomes were recorded. The biomarkers under study were complete blood count, renal profile, liver function test, creatinine phosphokinase and coagulation profile.

Results: Of the 178 consecutive patients, we had 80.9% females and 19.1% males with the mean age 22±8.48 years, whose mode of intoxication was suicide (95.5%). There was no significant change for biomarkers between males and females (p-value >0.001) but we found a significant difference for laboratory marker levels of patients when compared to reference range (p-value <0.001) for all, except Prothrombin time (p-value=0.28).

Conclusion: PPD poisoning has emerged as a newer trend set for committing suicide. Young females are more inclined to commit suicide through this means. It has devastating effect over various organs which is being manifested by significantly deranged various biomarkers.

Keywords: Biomarkers, Paraphenylenediamine, Poisoning, Suicide.

INTRODUCTION

Suicide is the act of intentionally causing one's own death. One of the preferred means of suicide is poisoning and it accounts for 30% suicides. Approximately a million people die worldwide annually because of suicide[1]. The global rate of suicide is 16/100,000 individuals.

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Every 40 seconds, one person on average dies by suicide somewhere in the world[2] and 1.8% of global deaths are due to suicide[3]. In the past 45 years, suicide rate have increased by 60%[4].

Exposure to pesticides or their ingestion is the most common poisoning noticed in the developing nations[5]. Noteworthy, hair dye poisoning is emerging as an important means of intentional self-harm. Paraphenylene diamine (PPD) a paranitroanaline derivative[6] and a synthetic aromatic amine, has a chemical formula $[C_6H_4(NH_2)_2]$ and a molecular weight of 108.15 g/mol is major constituent of the hair dye.[7] It is purely available in white crystal form which rapidly turns brown on air exposure and is also widely used in industries such as textile or fur dyes, dark colored cosmetics, temporary tattoos, photographic development and lithography plates,

photocopying and printing inks, black rubber, oils, greases and gasoline.[6]

PPD is commonly used in its raw form for cosmetic purposes in Africa, Middle East and Indian subcontinent while it is rarely used in the west[6,8] for the European Union and Food and Drug Administration authority have restricted its use in hair dye in the west[7]. Moreover, the countries where PPD is prepared consider it a potential health hazard now[6]. In our culture, PPD which is called kala-pathar (black stone)[9], used as an ingredient in hair dye so as to beautify women (or men) on social events to fasten their hair color[6,8,10], available at low cost[4].

Hair colorants have been used since centuries but first artificial dye was synthesized in 1856[4,10]. Moreover, PPD mixed with hydrogen peroxide have traditionally been used in hair dying since 1883[10]. Accidental as well intentional use of hair dye as a mode of suicide has been reported in Asian and African countries[4]. The first case of PPD poisoning was documented in 1924 in a hair salon owner[4,6,11]. PPD is a well-known skin irritant in susceptible individuals absorbed through dermis but systemic toxicity is established with its ingestion[11-12]. PPD poisoning has broad spectrum of adverse effects specifically targeting respiratory, renal, cardiac, neurologic, gastrointestinal and hematopoietic systems[4,13] and it has been reported to cause carcinogenic & mutagenic consequences as well[14].

The triad of fatal features characteristically encountered in PPD poisoning includes acute cervicofacial angioedema (upper airway obstruction manifesting with a hard swollen protruding tongue and edematous bull neck) followed by rhabdomyolysis and myoglobinuria with chocolate-color urine and acute renal failure[9,15]. The extent of renal involvement varies between transient proteinuria and oliguric acute kidney injury[16]. Other manifestations of PPD poisoning may include dysphagia, nasal regurgitation, abdominal pain, vomiting, tachycardia, seizures, intravascular hemolysis hemoglobinuria, metabolic acidosis, shock, muscular edema, leukocytosis, arrhythmias, hypocalcemia & hepatic necrosis[15-17].

Renal injury is considered to be a consequence of direct toxic effect of PPD, hematologic disruption and rhabdomyolysis[6,18]. Similar is the case for cardiotoxicity[6,19,20]. Increased free radical formation has been shown responsible for deleterious effects of PPD poisoning on tissues and the mechanism of deterioration of body symptoms secondary to PPD intoxication was described by many studies[6,11,15,21]. The systemic side effects produced by it are dose-dependent ranging between 2 to 10grams and varying with the potential susceptibility of the individuals[9,17,22]. A dose greater than 10grams was shown cardiotoxic and damaging to the myocardium[23]. Importantly, the concentration of PPD in hair dye varies among population[7,10].

The diagnosis of PPD poisoning is largely dependent on clinical manifestations. In many developing countries where laboratory facilities are lacking or absent, the clinical features are used in the diagnosis of PPD poisoning[6]. However, organ damage may be assessed by appropriate tests for rhabdomyolysis and hepato-renal involvement. There are various biochemical changes that occur in PPD poisoning like TLC in hematology; ALT with liver injury; urea, creatinine, myoglobinuria and hematuria for AKI; CPK for muscle damage and so on. This abnormal profile can help confirming the PPD intoxication and the extent of tissue damage. The urine can also be tested for PPD toxicity with the use of thin layer chromatography, essential in medico-legal reasons[6]. Though there is no antidote for PPD intoxication yet the condition is managed conservatively involving the use of emergency tracheostomy and endotracheal intubation, gastric lavage, ventilator support, fluid replacement, hydrocortisone, analgesics, antihistamines, dialysis, vasopressors, calcium gluconate and antiarrhythmic drugs[4,16]. The factors for poor prognosis following PPD poisoning have been documented in previous studies[16].

This study aims to analyze the laboratory findings and the extent of damage to various tissues following the PPD intoxication in Nawabshah, Pakistan.

MATERIAL & METHODS

Following the approval of ethical committee of the institute, the study was conducted in the Department of Medicine and Intensive Care Unit (ICU), Department of Anesthesiology, Peoples University of Medical and Health Sciences Nawabshah, Pakistan during October 2013 to October 2014. During the study, 178 consecutive patients were admitted to the ICU through Department of Medicine who had history of hair dye poisoning and were included in the study. After getting informed consent of the patients, the demographic, clinical and laboratory data was extracted from the specified charts. Data pertaining to the demographic features including age, gender, socioeconomic status and mode of intoxication were recorded. Clinical features were noted and laboratory findings and outcomes were also documented.

Laboratory data included complete blood picture i.e Hemoglobin, Total leukocyte and Platelet count, Prothrombin time. Liver function tests included levels of Bilirubin, Alanine aminotransferase (ALT) and Alkaline phosphatase (ALP). Renal function was assessed through Blood Urea, Serum Creatinine and Urine DR (hematuria). Muscle damage and rhabdomyolysis was assessed by obtaining Creatinine phosphokinase (CPK) levels. The reference range of the hospital laboratory is defined as: Hemoglobin 11-15 g/dL, TLC 4000-11000 cells/mm^3, Platelet count 150,000-450,000 cells/mm^3, Prothrombin time 14-14 seconds (Control), Bilirubin 0.6-1.2 mg/dL, ALT 7-41 U/L, ALP 33-306 U/L, Urea 14-50 mg/dL, Creatinine 0.7-1.2 mg/dL and CPK was 300-600 U/L.

The data was entered and analyzed using SPSS version-20. Continuous data was expressed in terms of mean±SD and a p-value of <0.001 was considered significant, whereas categorical data was illustrated as percentage (%).

RESULTS

There were 178 consecutive patients included in the study, of which, 80.9% (n=144) were females and 19.1% (n=34) were males consisting of age group between 4-55 years. The mean age was 22±8.48 years and more patients were between 15-25 years.

The mode of intoxication was suicide for 95.5% (170) whereas 4.5% (8) were accidental victims of PPD poisoning (Table-1). While the clinical features of PPD contain a variety. We found cervicofacial edema in 100% (178), difficulty in opening of mouth in 100% (178), dark urine in 82% (146), oliguria in 20.2% (36), myalgia in 67.4% (120), abdominal pain in 84.8% (151) and sinus tachycardia in 79.7% (142) victims (Table-2).

Most of the laboratory variables showed significant deviation from the reference values; however few were not changed markedly (Table-3). When these changes were compared between the two genders, there was no significant change observed (Table-4).

During management we needed tracheostomy for 74.2% (132) patients whereas 25.8 % (46) were managed conservatively without any surgical intervention. As for outcome is concerned, we lost 4.49% (8) patients, who were referred to different hospitals in Karachi, 16.86% (30) patients died and 78.65% (140) recovered and discharged (Table-5).

Table-1: Demographic Features of the Patients

Variable	Findings
Age	Age Group: 4-55 years Mean: 22+8.48 (76% between 15-25 years age)
Gender	Female: 80.9% Male: 19.1%
Mode of Intoxication	Suicidal: 95.5% Accidental: 4.5%

Table-2: Clinical Features of Victims of PPD Poisoning

Clinical Feature	Frequency	Percentage
Cervicofacial Edema	178	100
Difficulty in Opening of Month	178	100
Dark Urine	146	82
Myalgia	120	67.4
Oliguria	36	20.2
Abdominal Pain	151	84.8
Sinus Tachycardia	142	79.7

Table-3. Biomarker Levels in Patients Compared with Reference Range

Biomarker	Finding at Presentation (mean±SD)	Reference Range (mean±SD)	P-Value
Hemoglobin	11.22±2.03	14±2.01	0.000*
Total Leukocyte Count	14093±5307	9500±5028	0.000*
Platelet count	219048±78361	315000±137556	0.000*
Prothrombin Time	15.57±2.3	15±1	0.28
Bilirubin	1.03±0.49	0.50±0.50	0.000*
ALT**	478.4±616.4	24±17.1	0.000*
ALP***	269.8±136.2	169.5±137.3	0.000*
CPK****	23430±26372	451.7±151	0.000*
Urea	53.81±49.45	31.6±18.1	0.000*
Creatinine	1.48±1.5	1.0±0.00	0.000*

*P-value of <0.001 was considered significant
** ALT = Alanine Aminotransferase
*** ALP = Alkaline Phosphatase
**** CPK=Creatinine Phosphokinase

Table-4. Level of Biomarkers among Male & Female Victims

Biomarker	Finding at Presentation (mean±SD)	Reference Range (mean±SD)	P-Value*
Hemoglobin	12.3±2.23	11.01±1.89	0.23
Total Leukocyte Count	13665±75062	219491±79749	0.74
Platelet count	213353±75062	219491±79750	0.93
Prothrombin Time	14.76±0.9	15.76±2.5	0.85
Bilirubin	1.35±0.79	0.96±0..35	0.07
ALT**	578±578	456±630	0.39
ALP***	325±160	249±108	0.17
CPK****	22850±26493	23880±26570	0.11
Urea	46±40.6	55.6±51.7	0.17
Creatinine	1.12±0.33	1.58±1.26	0.07

*P-value of <0.001 was considered significant
** ALT = Alanine Aminotransferase
*** ALP = Alkaline Phosphatase
**** CPK=Creatinine Phosphokinase

Table-5. Measures & Outcomes of PPD Poisoning

Variables		Count	Percentage
Tracheostomy	Done	132	74.2
	Not Done	46	25.8
Outcomes	Died	30	16.86
	Recovered	140	78.65
	Referred	8	4.49

DISCUSSION:

Hair dye is emerging rapidly as a poison for suicide in this area. The constituents of this hair dye include PPD, propylene glycol, resorcinol, ethylene diaminetetraacetic acid (EDTA), liquid paraffin, sodium cetostearyl alcohol, herbal extracts, sodium lauryl sulphate, perfumes and preservatives.[22] Some of these ingredients are known toxins with multiorgan effects, while the toxicity profiles of others are not known.[24]

A number of studies have been published on hair dye poisoning with a suicidal intention.[5,17] These studies were focused more on clinical presentation and the outcomes of PPD intoxication. To the best of our knowledge, this is the first study from Pakistan analyzing demographic features and laboratory findings of the victims.

We had predominance of females (80.9%) in our study and almost similar findings were documented in many studies regionally and globally by Ayoub Filali et al.[25], M.Hamdouk[19], and PK Jainet al[26] with 77%, 80.7% and 74.86% respectively. Not only this but also ample literature supports this finding.[10] When the different variables were compared on gender basis, there were no significant changes observed. This shows that the poison affects both genders equally.

We had an age group of 4-55 years and the mean age was 22±8.48 with majority 76% of the patients between 15-25 years. Similar results were found in previous study consisting of patients in the group of 16-25 years [4] and a study by Raghu Kondle et al[22] concluded 23.8 ±7.8 mean age of the victims.

The mode of intoxication in our study consisted 95.5% being suicidal and finding of 84% was noticed in study by Suliman et al.[27] Mortality rate following the PPD ingestion in our study was 16.86%. However, the death rate varies in literature and it has been reported as 21.1% in a study[25] and 22% by Kerkeb et al[28]. According to a study by Abdelraheem et al[6]. These rates range from 12-42% and these variations could be attributed to multiple reasons including dose of PPD ingested, management protocol used, prompt access to the hospital and individual susceptibility[4,10-12,29].

We found significantly increased level of laboratory markers in our study as compared to the reference range with Hemoglobin, Total Leukocyte Count, Platelet count, Bilirubin, ALT, ALP, CPK, Urea and Creatinine with a p-value <0.001 but Prothrombin time was not significant (p-value=0.28).

In our study, TLC count was markedly raised (14093±5307) which is in almost near to the finding of 18960±5330 when more than 50 ml of poison was taken by victims in study of Raghu Kondle et al.[22]

Acute kidney injury has remained very fatal issue of the poisoning. Our study revealed increased urea level as 53.81±49.45 and creatinine as 1.48±1.5. The similar results were observed in a study conducted by NR Prasad et al.[30] where the levels were 62.54±59.2 and 2.55±2.85 respectively. However it differs from the study by Suliman et al[27] in which creatinine was 707µmol/L (7.9 mg/dl). This difference was because of the test in the study was done after 5 days of poisoning and the kidney damage of such extent is late manifestation in poorly managed patients. The chocolate colored urine was significantly observed in their study population which reflects the hematuria and myoglobinuria; the early markers of hemolysis and muscle necrosis.

CPK is another marker for rhabdomyolysis which is markedly raised in our study (23430±26372). This finding coincides with the studies conducted in the past.[10,22] PPD can bring about rhabdomyolysis by promoting calcium release and leakage of calcium ions from the smooth endoplasmic reticulum, followed by continuous contraction and irreversible change in the muscle's structure.[4] Rhabdomyolysis is the main cause of acute renal failure and the morbidity and mortality are high once renal failure develops[9].

The liver damage was assessed by the markers like ALT. It is markedly increased in our study. The mean increase is 478.4±616.4which is significant and it has also been observed in a study by Raghu Kondle et al[22] where the results were 991.58±1084.36. It signifies that acute hepatitis is

dose-dependent [9] and one of the early markers to be deranged along with TLC, CPK.

Hemoglobin, Platelet count, Bilirubin and Prothrombin time are not altered during initial course of the illness however they have been reported to be deranged lately[26,30,31].

CONCLUSION:

PPD poising has emerged as a newer trend for committing suicide in the vicinity of Nawabshah. It shows great influence on the laboratory markers indicating injury to important organ systems of the body. However, there is no gender related difference in these findings after the ingestion of PPD and interestingly, young females are more involved in such malpractice. Noteworthy, the condition is manageable with promptly taken steps.

We look forward to have histopathological studies in hair dye (PPD) poisoning so as to know the extent of tissue damage by the poisoning and can develop specific antidote.

LIMITATIONS OF OUR STUDY

As discussed previously, the PPD poisoning effects in a dose-dependent manner but we did not quantify the amount of hair dye ingested by the victims. Secondly, the time duration from ingestion of poison to clinical assessment has not been recorded in our study. Thirdly, the laboratory sampling was mostly done in early days of admission. These reasons might have led to the little variation in findings we had in contrast to what would have been observed in absence of these limitations. However, many of the results in our study were almost similar to the studies conducted in this geographic area in context to the PPD poisoning.

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