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Research Article

Incidence and Prognosis of Acute Lung Injury Following Acute Paraphenyline Diamine Poisoning

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Abstract: ***Background and Objectives:*** Hair dye poisoning emerging big problem in Upper Egypt. The main component of hair dye causing toxicity is para-phenylenediamine (PPD). The aim of the work: A prospective cohort study was planned to determine age, gender, route of administration, clinical manifestations and outcomes of the patients. Assess the relationship between the serum and urinary PPD levels with acute lung injury (ALI). ***Methods:*** The current study was conducted as a prospective cohort single-center study in Luxor International Hospital involving 40 patients diagnosed to have acute poisoning following hair dye ingestion in the period between January 2016 and July 2017. Diagnosis of ALI based on the presence of acute hypoxemia with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2: FiO2) of less than 400 mm Hg, bilateral infiltrates (including very mild infiltrates) seen on a frontal chest radiograph that is consistent with pulmonary edema. ***Results:*** Total number of cases enrolled in this study was 80, out of them 75% were females were in the age group of 18- 28 years. The intent of ingestion in our study was suicidal in 72.5%. The angioedema developed in all cases in deferent stages, dyspnea in 67.5%, cyanosis in 85%, black urine in 100%and lower limb pain, tenderness and myalgia in 77.5% due to rhabdomyolysis. Fits developed in 10% and circulatory shock in 10%.***Conclusions:*** PPD poisoning is multiorgan toxicity and fatal if not treated early.
Keywords: Hair dye poisoning,Paraphenylenediamine,Cervico-facial edema, Acute lung injury.

INTRODUCTION:

Para-phenylenediamine (PPD) substance is an aromatic amine known for its extreme sensitizing potency and may cause severe allergic contact dermatitis It is predominantly used as a precursor in oxidative hair dyes, but it can also be found in the so-called temporary henna tattoos, (Ragaa M. M. *et al.*, 2006). It is not found in nature and many industrial companies produce it commercially from coal tar (Ishaque, S. *et al.*, 2016).

PPD is derived from paranitroaniline which is highly toxic and used extensively in industrial products like colored cosmetics, tattoos, photocopying, black rubber oils and gasoline (Yagi, H. *et al.*, 1991). Para-phenylenediamine (PPD) is a typical chromophoric fixing in oxidative hair-colors. In some African nations like Sudan, Egypt, and Morocco yet in addition in India this substance is utilized alone or in a mix with shading extricates like Henna for coloring of the hair or the skin. Over the top dermal introduction to PPD essentially prompts the N-mono-and N, N′-diacetylated items (MAPPD, DAPPD) by N-acetyltransferase 1 and 2 (NAT1 and 2) catalyzed responses. Metabolites and PPD are chiefly discharged through renal freedom. In spite of an okay of inebriation when utilized in due structure, there are various instances of intense inebriation in those nations consistently. At the ENT Hospital - Khartoum (Sudan) alone over 300 cases are accounted for invariably (~10% lethal), for the most part, brought about by either an unplanned or expected (self-destructive) high foundational presentation to unadulterated PPD. Ingestion prompts severe clinical disorder including laryngeal edema, rhabdomyolysis, and ensuing renal disappointment, neurotoxicity, and severe harmful hepatitis. To date, there is no characterized clinical treatment or antitoxin accessible and treatment is to a great extent steady (Ishaque, S. *et al.*, 2016).

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PPD is known to have carcinogenic and mutagenic effects which are proved in animal studies, it causes allergic edema of tissues which may extend to angioneurotic edema, and it also causes a severe inflammatory response in the lung and consequently increasing capillary permeability and finally causing acute lung injury (Kallel, H. *et al.*, 2005).

AIM OF THE WORK

This study was planned to determine the incidence and prognosis of severe lung injury caused by the accidental or suicidal ingestion of stone hair dye containing Paraphenyline Diamine material.

PATIENTS AND METHODS

The current study was conducted as a prospective cohort single-center study in Luxor International Hospital involving 80 patients diagnosed to have acute poisoning following hair dye ingestion in the period between January 2016 and July 2017.

The inclusion criteria include a history of definite ingestion of hair dye, retrieval of the color from the gastric wash, Cervicofacial edema and the presence of black urine (indicating myoglobinuria due to tubular injury) whereas the exclusion criteria include history of chest disease or disseminated malignancy, failure to obtain blood or urine samples or history of ingestion of branded hair dye.

A detailed clinical history was recorded including demographic profile (name, age, gender, marital state), intention of poisoning, type of hair dye consumed, time interval between consumption of poison and first medical attention, nature of symptoms and clinical examination.

All patients were graded using the APACHE II Scoring System (Acute Physiology and Chronic Health Disease Classification System II) and The Sequential Organ Failure Assessment (SOFA) Score which predicts ICU mortality based on lab results and clinical data.

Diagnosis of acute lung injury based on the presence of severe hypoxemia with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2: FiO2) of less than 400 mm Hg (The oxygenation index is a calculation used in intensive care medicine to measure the fraction of inspired oxygen (FiO2) and its usage within the body) (Ortiz, R.M. *et al.*, 1987). Bilateral infiltrates (including very mild infiltrates) seen on a frontal chest radiograph. (Done by X-ray apparatus (554 800) that are consistent with pulmonary edema.

Serum and urine samples were collected from all patients on admission and after 48 hours of admission in survived patients to detect the paraphenylenediamine (PPD) and its metabolites [4-aminoacetanilide (MAPPD) and N_P_ phenyenebisacetamide (DAPPD)] levels. Blood samples were collected in EDITA containing tubes labeled with the subject identification number. Urine specimens were collected in clean, glass containers labeled with the subject identification number. All specimens were stored frozen below 20 degree centigrade. Samples then analyzed by High-Performance liquid chromatography (HPLC) kits for detection of P-phenylenediamine (PPD), 4-aminoacetanilide (MAPPD), N, N-P-phenylenebisacetamide (DAPPD), were purchased from Alpha Aesar, Thermofisher, Germany. Internal standard aniline (for synthesis) was purchased from research lab. Water was purified using a direct-Q gradient 8 UV system (Millipore). Dichloromethane, Acetonitrile was purchased from Carlo Erba group Inc. (HPLC grade). Hydrochloric acid, Ammonium solution 25% were from ADWIC. Potassium dihydrogen phosphate 99% was from Alpha Aesar, Thermofisher, Germany. Sodium hydroxide 97% was purchased from Alpha Aesar, Thermofisher, Germany. Stock solutions were prepared using 10mg analytical standard added to 10ml of 0.1% FA in water. 1ml of solution contains 1mg of Para-phenylenediamine, monoacetyl PPD and diacetyl PPD. For the calibration standards and quality control (QC) samples, the stock solution was diluted with 0.1% FA in water. Aniline was used as the internal standard and was dissolved in water.

For the preparation of the patient´s urine and blood samples from the clinic, 0.5 ml was hydrolyzed in 0.5 ml, 12N HCl for one h at 1000C and alkalized with conc. Ammonium hydroxide (Mohamed *et al.*, 2014). [40]The analytical method was validated to demonstrate linearity, the limit of detection (LOD) and limit of quantification (LOQ), accuracy and precision.

Management was supportive. Gastric lavage performed with activated charcoal. Endotracheal intubation was applied in cases with severe cervicofacial edema. Some cases failed intubations and undergone an emergency tracheostomy. Intravenous corticosteroids (Methylprednisolone), chymotrypsin, vasopressors, inotropes, intravenous amiodarone, defibrillation, forced diuresis by loop diuretics, sodium bicarbonate, adequate fluid therapy (10±4 liters/day), calcium gluconate, anticoagulants (LMWH) and antiplatelet. Dialysis- hemodialysis was used for cases with renal shutdown and resistant hyperkalemia.

Statistical Analysis

Data collection, patient's assessment, treatment, and follow-up were recorded. All results were expressed as mean ± SD. The mean values in different groups were tested using student t-test. The ROC curve. In a Receiver Operating Characteristic (ROC) curve the exact positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold; Data

were analyzed using SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA) and MedCalc version 15.8 (MedCalc© Software bvba, Ostend, Belgium).

RESULTS

A total of 88 patients with a history of poisoning were admitted to the ICU of Luxor International Hospital from January 2016 to July 2017. Among different types of poisoning 80 (90%) patients were of hair dye poisoning. (40 patients only had fulfilled the inclusion criteria) This prospective cohort study was conducted on 40 patients of hair dye poisoning, Patients having a history of mixed poisoning, ingested branded hair dye, with age more than 75 years old, and history of chest disease, e.g. COPD, asthma or with history of disseminated malignancies were excluded from the study.

The mean age of the studied patients was 25±11 years (ranged from 5 years to 57 years old). 72.5% had a definite history of suicidal attempt, 10% had a history of accidental ingestion while 17.5% denied ingestion of hair dye and suspected hair dye ingestion from the symptoms fifteen cases died (37.5%) and 25 cases (62.5%) survived. (Death was due to multiple organ dysfunctions)

In our study, all patients consumed local unbranded stone hair dye and couldn´t detect the volume of dye ingested as no accurate data from the patients or their relatives.

Comparison between serum and urinary level of PPD and its metabolites on admission and after 48 hours; Mean serum PPD level showed a gradual increase from 2µg/ml on admission to 3.3µg/ml after 48 hours. Mean serum MAPPD level was 15.5µg/ml on admission then increased to 19.1µg/ml after 48 hours. Mean serum DAPPD level was 56.5µg/ml on admission and became 66.1µg/ml after 48 hours.

Mean of the urinary PPD level showed a gradual decrease from 231.8µg/ml on admission to 22.8µg/ml after 48 hours. Mean urinary MAPPD level was 736.7µg/ml on admission then decreased to 38.2µg/ml after 48 hours. Mean urinary DAPPD level was 11776.8µg/ml on admission and became 1586.8µg/ml after 48 hours. (Figure 1and figure 2)

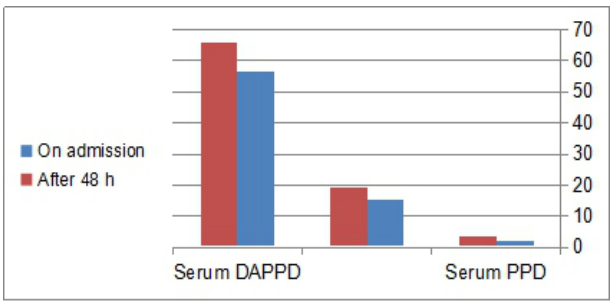

Figure.1 The mean serum PPD, MAPPD, and DAPPD on admission and after 48h

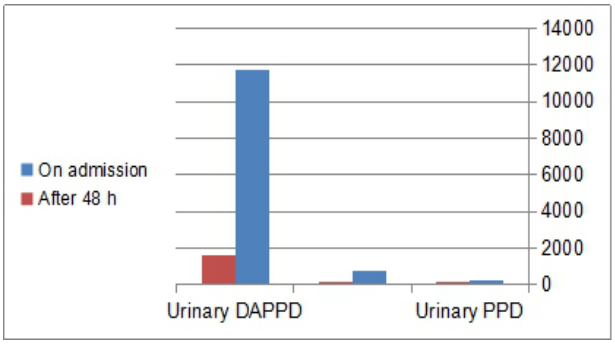

Figure.2 The mean urinary PPD, MAPPD and DAPPD on admission and after 48h

The mean time elapsed between ingestion and presentation is 11±11 hours (ranged from 5 hours to 72 hours).

The primary manifestation of PPD poisoning is facial and neck swelling which is divided into four stages:-Stage I, Patients with facial rash, facial edema, and lipedema (0 patients). Phase II, edema extended to the soft palate (8 patients 10%). Stage III, patients with lingual edema (10 patients 12.5%). Stage IV, Patients with laryngeal edema (62 patient 77.5%). (Staging according to the severity of systemic affection)

The angioedema was leading to upper airway obstruction which caused dyspnea in 27 cases (67.5%) and cyanosis in 34 cases (85%). Black urine in all cases (100%) and lower limb pain, tenderness and myalgia in 31 cases (77.5%) due to rhabdomyolysis. Fits developed in 8 cases (10%) with healthy CT brain. Only 8 cases (10%) developed circulatory shock. About 60% of cases developed ECG changes. (Table 1)

Table1: Clinical presentation of patients:

Clinical presentation	*No.of cases*	*%*
Dyspnea	27	67.5%
Cyanosis	34	85%
Black urine	40	100%
Lower limb pain and myalgia	31	77.5%
Fits	8	10%
circulatory shock	8	10%
ECG changes	24	60%

Table1: Different presentations of paraphenylediamine poisoining,

Twelve cases needed only face-mask O2, 62 cases treated by endotracheal tube. Two cases treated by tracheostomy and 1 cases treated by an endotracheal tube which failed to secure airway so replaced by tracheostomy. On admission, the PaO2/FiO2 ratio median NO. Was 355 on mechanical ventilation. So 34 cases required mechanical ventilation. The mean duration of mechanical ventilation was four days, and thirty cases developed ALI.

Forty cases (50%) had resolved CXR on discharge. The mean duration of mechanical ventilation was four days while the mean length of ICU stay (LOS) was six days. The strong association found between ALI and time elapsed between ingestion and presentation with statistically significant (p=0.001) with a cut of point >6 hours that could predict the occurrence of ALI with a sensitivity of 93.3% and specificity of 64%, Table (2), Figure (1).

Table 2: relation between ALI and time elapsed between admission and start of symptoms:

Parameter	Cut of Point	AUC	Sensitivity	Specificity	PPV	NPV
Time of admission from the start of symptoms	>6	0.807	93.33	64.00	60.90	94.10

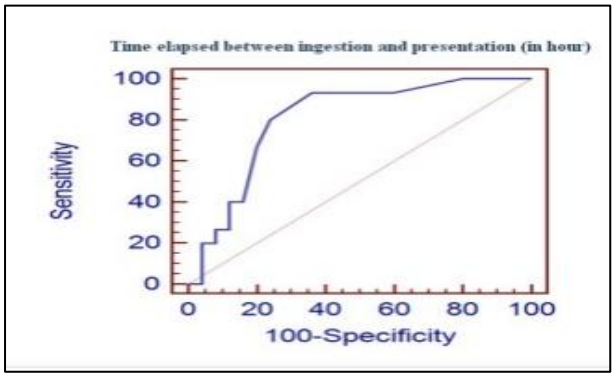

Figure (3): Roc Curve showed the relation between the ALI group and time elapsed between ingestion and presentation (an hour)

Correlation between time elapsed and survival: There was a statistically significant high correlation between time elapsed between ingestion and presentation (hr.) and survival (p=0.003) with a cut of point >6 hours that could predict mortality with a sensitivity of 93.3% and specificity of 64%.

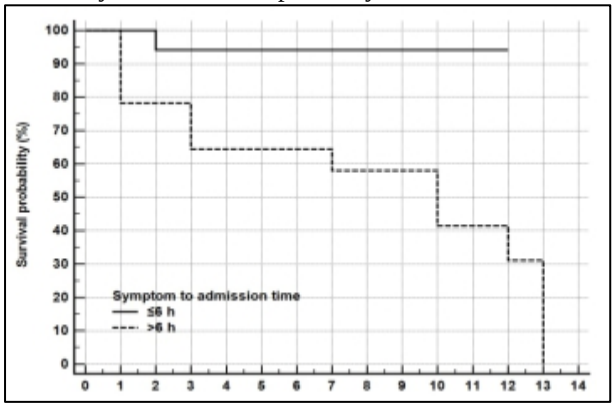

Figure (4) Kaplan-Meier survival curves with time elapsed between ingestion and presentation (an hour) ≤6 h or >6 h.The difference between the 2 curves is statistically significant (log-rank test p-value = 0.016, hazard ratio = 6.82, 95% CI = 2.32 to 20.04).

Chest x.ray of affected patients showedbilateral pulmonary infiltrates (figures 5-1 and 5-2 versus normal x-ray ,figure 5-3

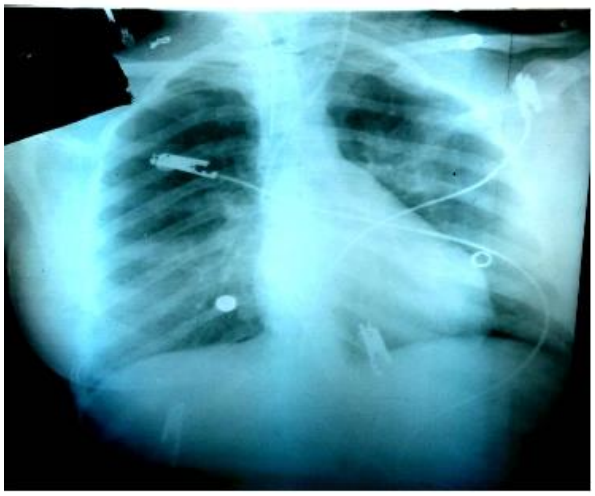

Figure (5-1): Chest x-ray during ICU stay. Female patient 16 years old, admitted to ICU after PPD poisoning. Chest x-ray on admission, there is mild bilateral infiltrations. During ICU admission she worth ARDS then she died.

Figure (s-2): Chest x-ray of a child on admission.

Figure (5-3): normal chest bronchogram

Acute Physiology and Chronic Health Evaluation II (APACHE II) score when applied on admission it showed statistically significant correlation with survival (p=< 0.001) and ALI (p= 0.007) that cases with a score more than 11 developed high

Mortality and predicted the occurrence of ALI. While after 48 hours of admission, it showed a statistically significant correlation with survival (p=< 0.001) that cases with score 9 or more developed high mortality. It was a statistically significant correlation with ALI (p=< 0.001) that score >7 predicted development of ALI.

Sequential organ failure assessment (SOFA) score when applied, it showed a statistically significant correlation with survival (p=<0.001), cases with score <3 or more developed morbidity. It was a statistically significant correlation with ALI (p= <0.001) that score >3 predicted development of ALI.

DISCUSSION

Stone hair dye is cheap and easily available in Upper Egypt, so it is used in hair dye and drawing skin tattoo on special occasions as weddings and in tourism places. Middle-aged females are the common group at risk of suicidal intent of PPD intoxication, mainly through oral ingestion. This was nearly the same number of patients recorded by Mohamed *et al.,* (2014) and Ramulu *et al.,* (2016) showed a female preponderance with 67.9%, 63.9%, 77%, 94.7%, 89%, 93.3%. And 80.64%respectively.

The majority of cases in the age group of 18-28 years old. Many researchers agreed with our results in their studied patients as Ramulu *et al.,* reported that the mean age of their studied patients was 24±8 (range 16-45 years) (Ramulu *et al.,* 2016).

The causes of committing that crime were mainly due to psychological problems, socioeconomic causes or failed to pass the exam. Concerning the manner of death, the intent of ingestion in our study was suicidal in 72.5%. Regarding the reason of poisoning, suicidal intention was identified in the studies carried by Mohamed *et al.,* (2014) to present 91.7%, 73. 7%, 86.7%, 94.74%, 100%, 97.84%, 91.7% and 95.7% respectively. Rawat *et al.,* reported that the psychological evaluation was found to be normal in all these patients. This indicates that most of the suicidal attempts were impulsively precipitated by either scolding from parents, family quarrels or socio-economic failure.

We found that time elapsed between ingestion and presentation in an emergency (hr.) was very important in which cases presented to an emergency within 6 hours showed good recovery according to GOS (p=0.003) and decreased occurrence of complications as ALI (p=0.001) and AKI (p=0.019). Our results were in accordance with that stated by Jain *et al.,* (2011). Discussed that time elapsed in seeking hospital admission, and early management influenced the mortality and morbidity. So we agreed with the above statement that early recognition and rapid intervention by secure airway, aggressive fluid therapy, gastric wash, and forced diuresis were the cornerstones of management.

PPD provokes prominent edema, which appears to be grossly specific and selectively localized in the head and neck. In our study, all cases presented with edema which developed in different stages. Majority of patients (77.5%) presented with wooden hard swollen protruded tongue with swelling of pharynx and larynx (stage 4), 12.5% of patients presented with stage 3 and 10% of patients presented with stage 2. The cervicofacial edema of our patients in accordance with the studied patients by Ramulu *et al.,* (2016)., who reported that most of their patients were in stage 2 and 3, while the rest were presented in stage 4 were 5 of which only one survived rest did not survive Raghu *et al.,* recorded cervicofacial edema with the thick protruding tongue was observed in 44 patients out of these 22 had difficulty in opening their mouth. They reported the duration of ventilator support was 6.19 ± 4.19 days (2012)**.** They reported that the cervico-facial swelling was the most common symptom (70.76%) involving the tongue, the floor of mouth, eyelids, and conjunctiva which may be due to the prolonged time of contact with oro-pharyngeal mucosa (Mohamed, K.M. *et al.,* 2014).

There is no statistically significant between the serum and urinary levels of PPD, MAPPD and DAPPD levels on admission or after 48 hours with the occurrence of ALI.ALI developed earlier because of upper airway obstruction. Senthilkumaran, S., & Thirumala, P. (2015), stated that PPD toxicity is due to some effect either on the blood colloids or vascular permeability. Furthermore, it was believed that the PPD toxicity is due to altered vascular permeability and involvement of the parasympathetic nervous system. Deamination and formation of analine are claimed to be responsible in part for the toxic symptoms (Jain, P. K. *et al.,* 2011).

CONCLUSION:

Poisoning by ingestion of hair dye is increasing at an alarming rate. This surge may be attributed to its cheap and readily available in almost all local general stores. It causes a severe form of acute lung injury and may be Further studies must be done to find effective antidotes against that aggressive rapidly killing poison. A programme of public education and restriction of PPD is urgently required in Upper Egypt and other affected nations.

LIMITATIONS OF THE STUDY

The Main Limitations Are: Being a single center study and the small number of studied patients.

RECOMMENDATIONS:

Extensive studies should be performed covering multiple centers to evaluate the prognosis and complications in Egypt. We also recommend multiple studies to state a protocol of management of PPD poisoning and to find effective antidotes against that aggressive rapidly killing poison. A program of public education and stricter control over the sale and distribution of PPD in Upper Egypt should go along towards alleviating this problem. Ingestion of large quantities of PPD can be fatal, and the physician should assess the patient for early detection and treatment of angioneurotic edema and cardiac arrhythmias.

REFERENCES

1. Ragaa M. M., Madeha M. M., Makhlof., & Manal M.S.El-Meligy. (2006). "Systemic effects of ingestion of hair dye: An experimental study " The 2nd Int. Conf. for Develop. And the Env. In the Arab world, March, (21), 23.
2. Ishaque, S., Haq, A., Jurair, H., & Siyal, H. (2016). Kaala Pathar (Paraphenylene Diamine) Poisoning and Angioedema in a Child: An Unusual Encounter. J Clin Toxicol 6, 294.
3. Yagi, H., el Hind, A. M., & Khalil, S.I. (1991). "Acute poisoning from hair dye". East Afr Med J. 68(6), 404-11.
4. Kallel, H., Chelly, H., Dammak, H., Bahloul, M., Ksibi, H., Hamida, C.B., Chaari, A., Rekik, V., Debore, M. E., & Bouaziz, M. (2005). "Clinical manifestation of systemic para-phenylenediamine intoxication." J. Nephrol, 18, 308-311.
5. Ortiz, R.M., Cilley, R.E., & Bartlett, R.H. (1987). Extracorporeal membrane oxygenation in pediatric respiratory failure. Pediatr Clin North Am, 34(1), 39-46.
6. Mohamed, K.M., Hilal, M.A., & Nady, S. Aly. (2014). Fatal Intoxications with Para-Phenylenediamine in Upper Egypt. Int J Forensic Sc.
7. .Rawat, R., Kumar, M., Singh, P.S., Kumar, G., & Verma, V. (2016). Study of hair dye poisoning and its outcome in tertiary care rural institute. Int J Res Med Sci, 4, 3240-4.
8. Jain, P. K., Agarwal, N., Sharma, A. K., & Akhtar, A. (2011). Prospective study of ingestion hair dye poisoning in Northern India (Prohina) Journal of Clinical Medicine and Research, 3(1), 9-19.
9. Raghu, K., Rama Mohan, P., Satish, K. S., Srinivas, M., & Veera, P. M. (2012). "Clinical Profile and Outcomes of Hair Dye Poisoning in a Teaching Hospital in Nellore." International Scholarly Research Network ISRN Emergency Medicine, Article ID 624253, five pages doi:10.5402/2012/624253.
10. Ramulu, P., Rao, P.A., Swaroop, K.K., Marx, P.K., & Devi, C.V.R. (2016). A prospective study on clinical profile and incidence of acute kidney injury due to hair dye poisoning. Int J Res Med Sci Pathol, 2(3), 19-23.
11. Senthilkumaran, S., & Thirumala, P. (2015). Acute hair dye poisoning: Lurking dangers. J Mahatma Gandhi Inst Med. Sci, 20, 33-7.