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Research Article

A Prospective Study to Assess the Severity and Outcome of Poisoning with Auramine-O and Malachite Green Dye

Mohamed Hisham[1]*, Sakthivel Murugesan[2], Lakshmikanthcharan S[2] and MN Sivakumar[2]

[1]Critical Care Clinical Pharmacist, Department of Critical Care Medicine, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India

[2]Consultant Intensivist, Department of Critical Care Medicine, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India

***Corresponding Author:** Mohamed Hisham, Critical Care Clinical Pharmacist, Department of Critical Care Medicine, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India.

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Abstract

Auramine-O and malachite green are toxic dyes commonly used in southern part of India. There is inadequate data on poisoning with these toxic dyes. Our aim was to assess the severity and outcome of poisoning with auramine-O and malachite green dye. This single centered; prospective cohort study was conducted over a period of four years in a 30 bedded medical and surgical intensive care units (ICU) of a 750 bedded multi-specialty, tertiary care hospital in south India. All synthetic dye poisoning patients admitted to the ICU from January, 2011 to December, 2015 were included in the study. Patients discharged against medical advice and who consumed other poisons in combination with synthetic dye were excluded. A total of 61 patients were enrolled in our study, out of which 53 patients (mean age, 33.1 years; 73.5% female). It was further categorized as auramine-O poisoning [n = 44 (83.1%)] and malachite green poisoning [n = 9 (16.9%)]. Prolonged n- acetylcysteine infusion improved hepatic function in 78.9% (n = 15/19) patients with raised hepatic aminotransferases. The benefits of early presentation to the hospital after toxin ingestion were overshadowed by severe poisoning which reduces the possibility of survival. Mortality was higher with malachite green poisoning [n = 1/9 (11.1%)] compared to auramine-O poisoning [n = 3/44 (6.8%)]. Four non- survivors (7.5%) in our study had intractable arrhythmias, hypotension, refractory status epilepticus and severe metabolic acidosis which led to cardiac arrest. The study underlines the clinical manifestations of both auramine-O and malachite green dye poisoning. This study provides evidence for clinicians on the severity and extent of toxicity due to these dyes. Additionally, the study emphasizes the use of prolonged n-acetyl cysteine infusion to reduce hepatotoxicity associated with synthetic dye poisoning.

Keywords: *Hepatotoxicity; Poisoning; Synthetic Dye*

Abbreviations

ACLS: Advanced Cardiac Life Support; AHA: American Heart Association; hr: Hour; ICU: Intensive Care Unit; INR: International Normalized Ratio; IQR: Interquartile Range; kg: Kilogram; mg: Milligram; NAC: n-Acetylcysteine; n: Number; SE: Standard Error; %: Percentage

Introduction

Auramine-O (yellow - diarylmethane dye) and malachite green (green - diphenylmethane dye) are toxic dyes commonly used in southern part of India to clean temple premises and courtyards of houses during festive occasions [1]. This synthetic dye has an odour similar to cow dung and there exists a myth that it has germicidal property. It is popularly known as 'Sani powder' or 'cow dung powder' in the

state of Tamil Nadu, India. Though the sale of this toxin is legally banned [2], it is still freely available in the shops as packets of 25 grams.

Synthetic dye ingestion commonly causes yellow or green skin discoloration based on the compound. Auramine-O poisoning is mainly neurotoxic and hepatotoxic. Other ramifications of poisoning may vary from nausea, vomiting and abdominal pain in milder forms to toxic hepatitis, metabolic acidosis, generalized tonic- clonic seizures and status epilepticus in severe varieties. Non-significant and delayed rise in hepatic aminotransferases is considered as mild poisoning. Malachite green poisoning is highly toxic and causes multi- organ failure [3]. In severe poisoning, patients present with three or more of the following complications which include refractory status epilepticus, intractable arrhythmia, hypotension, five times rise in hepatic aminotransferases, acute kidney injury and refractory metabolic acidosis. Mortality associated with severe poisoning results from refractory circulatory shock and cardiac arrhythmias.

However, only scanty data are published regarding the severity of poisoning with auramine-O and malachite green in humans [4,5]. The purpose of this study was to assess the severity and outcome of poisoning with auramine-O and malachite green dye.

Materials and Methods

Study design

This is a single centered, prospective cohort study conducted over four years in the 30 bedded medical and surgical intensive care units (ICU) of a 750 bedded multispecialty tertiary care hospital in south India. Synthetic dye poisoning management protocol was created to serve as a guiding document for physicians.

Study population

All patients with synthetic toxic dye poisoning requiring ICU admission from 1st January, 2011 to 31st December, 2015 were registered in the study, irrespective of their age. Patients who consumed other poisons in combination with synthetic dye and who were discharge against medical advice during the study period were excluded from the study.

Management protocol for synthetic dye poisoning

Synthetic dye poisoning is lethal with no available antidotes. Management includes appropriate organ support. Gastric lavage is given if the patient presents to hospital within one hour of toxin ingestion. Activated charcoal and whole bowel elimination techniques are not effective decontamination methods in this poisoning. Acute poisoning associated with toxic hepatitis is routinely managed with n-acetylcysteine (NAC) infusion. The dosing regimen includes an initial loading dose of 150 mg/kg of NAC over one hour, followed by 12.5 mg/kg/hr for 4 hours, then continuous infusion of 6.25 mg/kg/hr until endpoints are achieved. Endpoints for discontinuation of NAC infusion include improvements in hepatic aminotransferases and other prognostic markers like lactate, prothrombin time and international normalized ratio (INR). Seizures are managed with lorazepam and levetiracetam. Refractory status epilepticus is managed with phenobarbital and continuous infusion of midazolam. Cardiac arrhythmias are managed as per American heart association (AHA) advanced cardiac life support (ACLS) protocol.

Outcome measurements and data collection

We collected data from various sources including medical records, laboratory data, treatment chart, direct patient interview and sometimes by interacting with treating clinician. We reviewed hospital medical record for information on demographics, quantity of poison ingested, time lapse since ingestion to commencement of treatment, management at outside hospital, presenting signs and symptoms, treatment, complications and outcome. The study also recorded the organ dysfunctions, duration of ventilation, length of ICU stay and duration of hospitalization. For any non-survivors during the study, we documented the cause of death from the medical death certificate. The institution ethics committee approved the study (registration number EC/AP/147/04-2011) and waived informed consent from all study participants.

Statistical Analysis

Categorical variables were expressed as frequency (percentage); continuous variables were described as mean values with standard error. The differences in categorical variables were calculated using Fisher exact test. Statistical significance was defined as p- value less than 0.05 for a confidence interval of 95%. All statistical analyses were performed with SPSS software (SPSS, version 23; IBM Corp., Armonk, NY).

Results and Discussion

Inadequate data on poisoning related to auramine-O and malachite green dye, necessitates to study the severity and outcome associated with this toxic dye ingestion [6]. Sixty- one patients were enrolled in the study; eight patients did not meet the inclusion criteria due to discharge against medical advice and multiple toxin ingestion along with synthetic dye poisoning. Among the 53 patients included in the study; mean [standard error (SE)] patient age was 33.1 (2.1) years [interquartile range (IQR) 23 - 37 years] and 73.5% (n = 39) of the patients were women. The incidence of the synthetic dye poisoning among the age group were 35.8% in 20 - 29 years (n = 19) and 26.4% in 30 - 39 years (n = 14). The type of synthetic dye poisoning was found to be 83.1% auramine-O (n = 44) and 16.9% malachite green (n = 9). By profession, majority of the poisoning patients were 52.8% housewives (n = 28) followed by 15.1% students (n = 8).

The proportion of patients who reported to have consumed more than 50 gm (two packets) of toxin were 26.4% (n = 14), less than 50 gm of toxin ingestion were 35.8% (n = 19) and the remaining 37.7% (n = 20) patients consumed unknown quantity of toxin. Of the 53 patients, 77.4% patients (n = 41) presented directly to our hospital and got treated. Remaining 22.6% patients (n = 12) received first aid elsewhere and later referred to our hospital. Patients who presented within two hours of poisoning to our hospital were 49.1% (n = 26) and 26.4% (n = 14) presented between two to six hours of toxin ingestion. The benefits of early presentation to the hospital after toxin ingestion are overshadowed by severe poisoning which reduces the possibility of survival (Table 1).

	Death (%)	
	Yes	No
Hospital admission within two hours of toxin ingestion	3/4 (75)	23/49 (46.9)
Quantity of toxin ingested more than 50 gm	2/4 (50)	12/49 (24.5)
Features on hospital admission		
Severe Poisoning	4/4 (100)	2/49 (4.1)
Skin Discoloration	4/4 (100)	31/49 (63.3)
Seizures	4/4 (100)	6/49 (12.2)
Transaminitis	4/4 (100)	15/49 (30.6)
Acute kidney injury	2/4 (50)	3/49 (6.1)
Arrhythmias	4/4 (100)	3/49 (6.1)
Hypotension	2/4 (50)	2/49 (4.1)
Metabolic acidosis	3/4 (75)	3/49 (6.1)

Table 1: *Mortality outcome and characteristics of synthetic dye poisoning.*

In this prospective study, 66.1% (n = 35) patients had skin and mucous membrane discoloration over the face, neck, upper abdomen, upper and lower limbs (Figure 1-3). This was not fully explained by the spillage of the powder on the skin. The toxin being excreted through the skin could be a possible explanation for this generalized skin discoloration. Extensive toxin distribution to the tissues in the unionized state could be a reason for discoloration of body fluids especially urine in some of our patients [7]. Qualitative tests of blood

samples, gastric lavage samples and synthetic dye products were done in accredited toxicology screening and analytical laboratories. These samples detected the presence of malachite green and auramine-O; it was negative for the presence of any other toxins like copper or iron compounds.

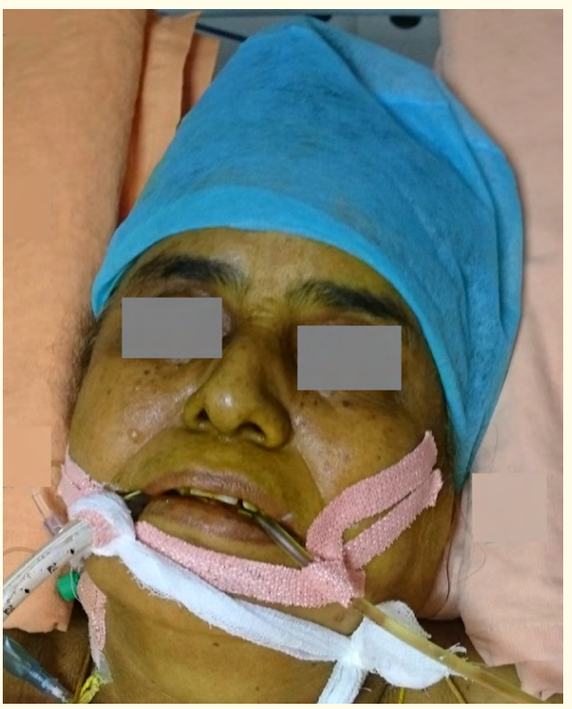

Figure 1: *Skin discoloration on the face after Auramine-O dye poisoning.*

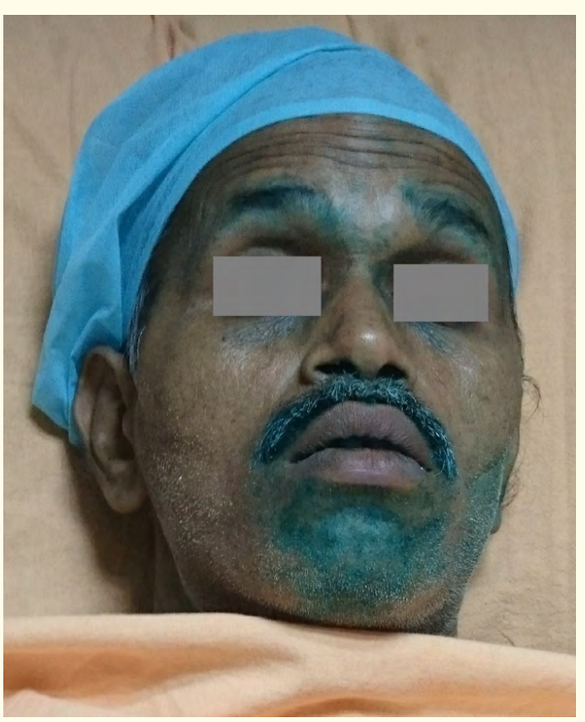

Figure 2: *Skin discoloration on the face after Malachite green dye poisoning.*

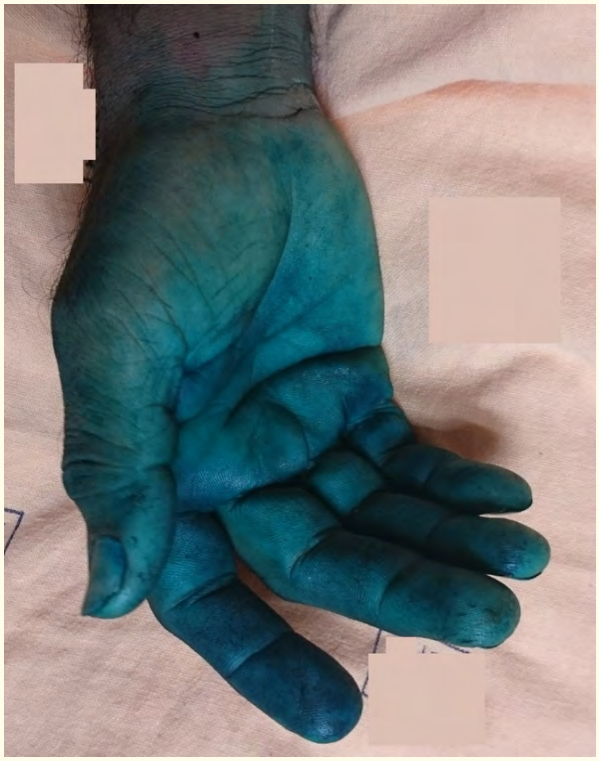

Figure 3: *Skin discoloration on the upper limb after Malachite green dye poisoning.*

The primary symptoms on admission were 67.9% (n = 36) gastrointestinal which included nausea, vomiting and abdominal pain. The most common finding was rise in hepatic aminotransferases observed in 35.8% patients (n= 19). NAC is a pro-drug of L-cysteine which acts as a precursor to the biological anti-oxidant glutathione. Administration of NAC infusion replenishes the glutathione stores and limits the injury to liver. Interestingly, among the 19 patients with deranged hepatic function (measured by raised hepatic aminotransferases), 78.9% (n = 15) patients demonstrated improved hepatic function within few days following prolonged NAC infusion. There is no literature evidence for using NAC infusions in dye poisoning. However, many studies and some recommendation favor use of NAC infusions in non-acetaminophen induced acute liver failure [8,9].

Ten patients (18.9%) presented with convulsions requiring anti- epileptic drugs. Nine patients (16.9%) required endotracheal intubation due to refractory status epilepticus or low Glasgow coma scale. The hepatotoxicity and neurotoxicity encountered in our patients were reported previously in few isolated case reports [1,10].

This study provides evidence of renal failure caused by synthetic dye ingestion. We reported five patients (9.4%) with acute kidney injury on ICU admission and three patients required hemodialysis. Renal biopsy was done in a patient in view of non- improvement in renal function. The finding was suggestive of toxic tubular necrosis and the patient responded to prednisolone therapy. Acute kidney injury associated with this poisoning requiring dialysis or steroid therapy is uncommon. In survivors with mild renal impairment the renal function improved following resolution of their acute illness. Some researchers discussed that unionized dye gets precipitated in the renal tubules resulting in acute kidney injury [7]. Hence, they suggested the usefulness of urine alkalinization for enhancing toxin elimination.

The mean (SE) length of ICU stay was 2.38 (0.55) days and mean (SE) length of hospitalization was 5.09 (0.62) days. Survival rate in our study was 92.5%. The probability of survival was inversely proportional to the severity of poisoning. Mortality was higher with malachite green poisoning [n = 1/9 (11.1%)] compared to auramine-O poisoning [n = 3/44 (6.8%)] as defined in table 2. Four non- survivors (7.5%) in our study had intractable arrhythmias, hypotension, refractory status epilepticus and severe metabolic acidosis which led to cardiac arrest. All patients with arrhythmias and cardiac arrest in severe dye poisoning were refractory to anti- arrhythmic drugs, cardioversion or defibrillation. The severity of synthetic dye poisoning based on the clinical presentations helps the clinician to counsel the patient's relatives on their prognosis and anticipate appropriate problems [11]. Long- term complications were not reported among patients who recovered from synthetic dye poisoning.

	Death (%)	
	Yes	No
Auramine-O dye poisoning	3/44 (6.8)	41/44 (93.2)
Malachite green dye poisoning	1/9 (11.1)	8/9 (88.9)

Table 2*: Mortality outcome in different synthetic dye poisoning.*

A limitation of this study was that it was a single centered study. The limited population enrollment is acceptable considering the rarity of poisoning and lesser referrals to tertiary care hospital [12]. A question for future research includes determining the lethal dose of the toxin and mechanism of toxicity associated with these synthetic dyes. It is important to identify patients who might worsen at presentation to the hospital. Further studies are required to explore different treatment options and to maximize recovery after toxin exposure.

Conclusions

In summary, this study highlights the clinical manifestations of both auramine-O and malachite green dye poisoning. The study findings provide evidence for clinicians on the severity and extent of toxicity due to auramine-O and malachite green dyes. Patients with severe poisoning presents with three or more of the following complications which include refractory status epilepticus, intractable arrhythmia, hypotension, five times rise in hepatic aminotransferases, acute kidney injury and refractory metabolic acidosis. Mortality is high in patients with severe poisoning. Additionally, the study emphasizes the use of prolonged n-acetyl cysteine infusion to reduce hepatotoxicity associated with synthetic dye poisoning. Public health authorities may need to reinforce the ban on sale of these lethal toxins.

Acknowledgements

Nil.

Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Bibliography

1. Hisham MD., *et al*. "Auramine-O and malachite green poisoning: Rare and fatal". *Indian Journal of Pharmacy Practice* 6.4 (2013): 72-74.
2. Avinash., *et al*. "'Sani' powder poison - Legally banned". *International Journal of Science and Research* 6.9 (2016): 101-109.
3. Culp SJ. "Mutagenicity and carcinogenicity in relation to DNA adduct formation in rats fed leucomalachite green". *Mutation Research* 506-507 (2002): 55-63.

4. Parodi S., *et al*. "DNA damage induced by Auramine O in liver, kidney, and bone marrow of rats and mice, and in a human cell line (alkaline elution assay and SCE induction)". *Journal of Toxicology and Environmental Health* 9.5-6 (1982): 941-951.

5. Srivastava S., *et al*. "Toxicological effects of malachite green". *Aquatic Toxicology* 66.3 (2004): 319-329.

6. Layland FC., *et al*. "Miscellaneous Poisoning in Children". Jaypee Publishers: New Delhi (2006).

7. Senthilkumaran S., *et al*. "Synthetic cow dung powder poisoning: Therapeutic aspects". *Indian Journal of Critical Care Medicine* 20.2 (2016): 128-129.

8. Lee WM., *et al*. "Intravenous n-acetylcysteine improves transplant free Survival in early stage non-acetaminophen Acute liver failure". *Gastroenterology* 137.3 (2009): 856-864.

9. Siu JTP., *et al*. "N-acetylcysteine for non-paracetamol (acetaminophen) - related acute liver failure". *The Cochrane Database of Systematic Reviews* 3 (2016): CD012123.

10. Sherfudeen KM., *et al*. "Cow dung powder poisoning". *Indian Journal of Critical Care Medicine* 19.11 (2015): 684-686.

11. Karikalan T., *et al*. "Profile of poisoning cases in a tertiary care hospital, Tamil Nadu". *Journal of Evolution of Medical and Dental Sciences* 3.56 (2014): 12754-12760.

12. Bastia BK., *et al*. "A Rare Case of Fatality due to Auramine Poisoning". *Journal of Indian Society of Toxicology* 1.1 (2005): 25-27.

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