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Effect of Henna-Induced Pigment Nephropathy on Kidney Outcomes: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Henna is extracted from a plant with scientific name of lawsonia intermis (Lawsonia alba) that is used for hair dye and fortified henna which is used for tattooing. The aim of this research was effect size assessment of henna on kidney outcomes.

Methods: In this systematic review and meta-analysis, thirty patients with henna and kidney impairment were considered. Clinical presentation, biochemical data, imaging, therapeutic modalities and follow up of data of patients were investigated. Prevalence rate of categorical variables was assessed with frequency and percentage and continuous variables with mean and median. Effect size of henna-induced pigment nephropathy was assessed using mean difference by Cohen's d test.

Results: In this study, nine out of thirty patients had history of topical/inhalational and twenty-one (70%) consumed swallowed mixed henna with paraphenylenediamine via various hair dyes or traditional alternative medicine. Para-phenylenediamine was detected in urine of 10% of patients using thin layer chromatography (TLG) and thin layer chromatography-gas chromatography/mass spectrometry (TLC-GC/MS) method. Three patients developed acute kidney injury (AKI) and one patient acute kidney disease (AKD) during follow up. Effect size of elevated serum creatinine based on the last serum creatinine measurement or the last serum creatinine measurement on dialysis modalities using standardized mean difference by Cohen's-d law was 1.637 (large effect). The mean average of pre-hemodialysis serum creatinine level and post-hemodialysis serum creatinine level was 7.04±4.90 and 4.59±3.06 mg/dl, respectively. Comparison between two variables using paired t test was assessed with *p*-value of 0.37. Nine out of thirty patients died in the present research.

Conclusion: Henna-induced pigment nephropathy is a disease due to hair-dye consumption**.** Hair dye related AKI and AKD was seen in 10% and 3.3% of patients, respectively. Effect of mixed henna on kidney outcome was assessed large in this research. Furthermore, the current research revealed high mortality proportion in henna users. Attaining to zero death in mixed henna-induced pigment nephropathy is a target.

Keywords: Henna, Dye-Related Acute Kidney Injury, Para-Phenylenediamine, Kaplan-Miere Analysis

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تأثير اعتلال الكلية الصباغي الناجم عن الحناء على نتائج وظائف الكلى: مراجعة منهجية وتحليل تلوي

فاطمة شامخي أميري

ملخص الدراسة

المقدمة: يتم استخراج الحناء من نبات يحمل الاسم العلمي لاوسونيا إنترميس (لاوسونيا ألبا) التي تستخدم لصبغ الشعر والحناء المدعمة التي تستخدم للوشم. يهدف البحث إلى التحقق في حجم تأثير الحناء على نتائج وظائف الكلى.

المنهجية: تمت مراجعة دراسات من نوع الدراسة التحليلية (التجريبية) المستقبلية مع تصميم التجارب السريرية العشوائية وكذلك من نوع المراجعة المنهجية والتحليل التلوي، حيث تم النظر في ثلاثين مريضا يعانون من الحناء وضعف الكلى. تم أولاً فحص العرض السريري والبيانات الكيميائية الحيوية والتصوير والطرائق العلاجية وبيانات المتابعة للمرضى. ثم تم تقييم انتشار وحجم تأثير اعتلال الكلية الصباغي الناجم عن الحناء.

النتائج: في هذا السياق، كان لدى 9 من 30 مريض تاريخ من الحناء الموضعية / الاستنشاقية أو ابتلاع الحناء المختلطة مع بارافينيلين دیامین (70٪) في صبغات الشعر المختلفة، والطب البديل التقليدي. تم الكشف عن بارا فينيلين دیامین في بول ثلاثة من المرضى باستخدام كروماتوغرافيا الطبقة الرقيقة (TLG) وكروماتوغرافيا كروماتوغرافيا الغاز ذات الطبقة الرقيقة / قياس الطيف الكتلي (MS / GC-TLC). ثلاثة مرضى تطور لديهم إصابات كلى حادة، و مريض واحد وجد عنده مرض كلى حادة أثناء المتابعة في البحث الحالي. تم تقييم العلاقة بين ارتفاع الكرياتينين في الدم ووقت انخفاض وظائف الكلى باستخدام قانون كوهين على أساس متوسط الفرق 1.16 (تأثير كبير). تم تقييم متوسط الكرياتينين المرتفع في المصل قبل الغسيل الدموي للكلى وما بعده كالتالي 4.90±7.04 و 3.06±4.59 ملغم / ديسيلتر. تم تقييم المقارنة بين متغيرين باستخدام اختبار t المزدوج بقيمة $p = 0.37$ وقد توفي تسعة من المرضى.

الاستنتاج: اعتلال الكلية الصبغي الناجم عن الحناء هو مرض ناتج عن استهلاك صبغة الشعر. شوهدت إصابات الكلى الحادة ومرض الكلى الحاد المرتبط بصبغة الشعر عند 10٪ و 3.3٪ من المرضى على التوالي. كشفت الدراسة الحالية أن هناك تأثير كبير للحناء على نتائج وظائف الكلى وكذلك ارتفاع نسبة الوفيات بين مستخدمي الحناء. الهدف هو عدم حدوث وفيات عند مرض الكلى الصبغي المختلط المرتبط باستخدام الحناء.

الكلمات المفتاحية: الحناء ، إصابة الكلى الحادة المرتبطة بالصبغة ، بارا فينيلين دیامین، تحليل كابلان مير

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Introduction

Henna is extracted from a plant with scientific name of lawsonia intermis that its dye is arisen from dried leaves of flowering herb [1]. The first time, Nott investigated systemic poisoning by hair dye in 1924 in middle age male [2]. Phytochemical screening of the Lawsonia intermis leaf extracts had showed the presence of glycosides, phytostereol, steroids, saponins, tannins and flavonoids [3]. It is used for tattooing or hair, hand and sole colors in regional and cultural utilities in Asia, Africa and Middle East. It contains para-phenylenediamine (PPD) that is called kala pathar in Pakistan. In Nigeria, henna plant with Yoruba name is used for cosmetic and medicinal purposes. The major material in henna plant is 2-hydroxy-1, 4-napthoquinone with name of lawsone that is used for treatment of diabetes in traditional medicine [4]. PPD metabolites include 4-aminoacetanilide (MAPPD) and N, N_P_phenyenebisacetamide (DAPPD) levels [5]. These compounds comprise different toxicities such as cardiotoxicity, hepatic necrosis, angioneurotic edema, rhabdomyolysis, acute renal failure (ARF) [henna in mixture with PPD], and multiple organ failure [6] [Fig.1].

Lethal dose of PPD is not known but is reported 7-10 gram as such in a case report, lethal dose of PPD was reported 10 gram [7].

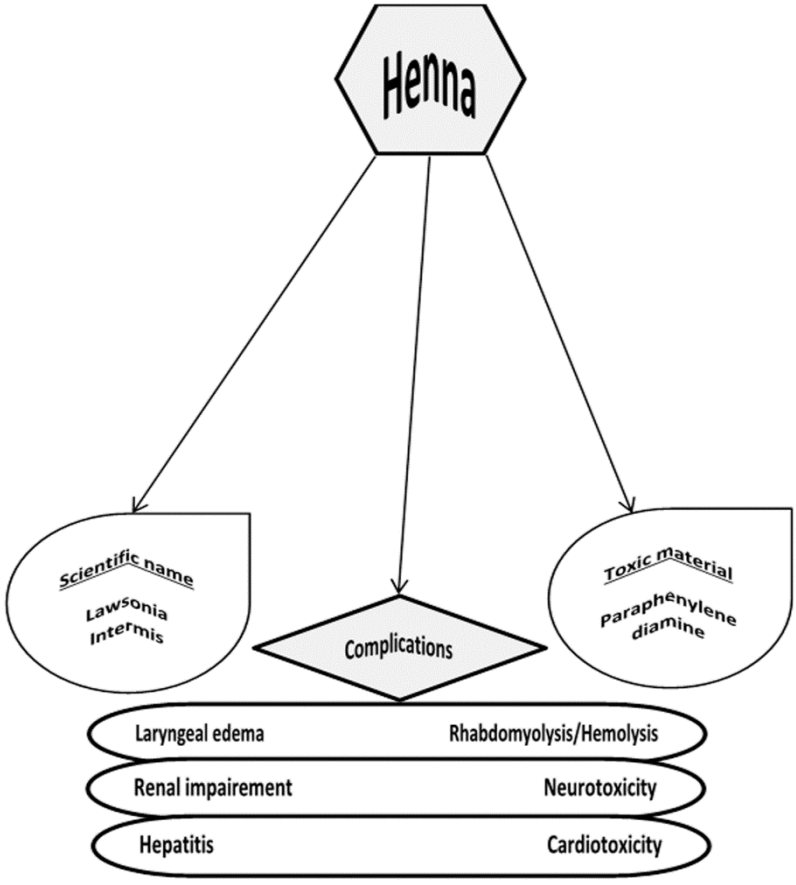

Fig. 1. Characteristics of Henna Herb

How does henna works on disturbed kidney?

Henna is reported as immunostimulant and chief constituents of henna are flavonoids. When henna is combined with PPD for acceleration of its effect, acute toxicity occurs [8]. PPD is highly toxic substance that is used in industrial products and chromophoric fixing in oxidative hair-colors. PPD and metabolites are principally excreted through kidney. Subsequently rhabdomyolysis and kidney failure can cause toxicity due to mixed henna. These toxic agents apply their effects on skin topically and/or ingestion. Furthermore, mixed henna cause toxic rhabdomyolysis that eventually culminate in to acute kidney injury while intravascular hemolysis and interstitial nephritis lead to renal injury. Tubulopathy is due to acute tubular necrosis, myoglobin casts and met-hemoglobinemia. Herbal toxicity for hair dye is increasing as such it accounted as an alarming bell. Awareness of toxic henna effect in creating renal complications causes early diagnosis and proper management. Herein, preventive modalities comprise avoidance of the hair dye, attaining to zero preventable deaths and limiting PPD sale. Therefore, the aim of this study is to investigate the effect size of henna on kidney function**.**

Methods

Eligibility Criteria

Type of Studies

Among screened 5261 full-text articles obtained in this research paper, 5186 articles were excluded due to unrelated subject, review articles and other studies. Then 75 full-text articles were eligible and 49 articles were excluded due to non case reports (n=49) in this research. All case reports were obtained via electronic search in PubMed central (PMC), PubMed, Scopus, Embase and Google Scholar databases. These 26 articles included 30 case reports that were examined 30 patients with henna usage and renal impairment for systematic review and meta-analysis synthesis.

Type of Participants

Patients with henna usage (topical or oral) and kidney impairments [acute kidney injury (AKI), acute kidney disease (AKD), chronic kidney disease (CKD) and non-kidney disease (NKD), kidney failure with replacement therapy (KFRT)] were enrolled in this research.

Type of Outcomes

Primary end-points

Effect of henna on kidney disturbances was assessed in this research. This kidney impairment encompass AKI, AKD, CKD, NKD, kidney failure progression to kidney replacement therapy. Persistent KFRT and death were another primary end-points.

Secondary end-points

Elevated serum creatine phosphokinase (CPK), serum creatinine (SCr) changes with dialysis were accounted as secondary end-points.

Information Sources

The paper has been written based on advanced searching via PubMed Central (PMC), PubMed, Scopus, Embase and Google Scholar databases to identify articles published from inception to December 2022.

Search methods for identification of studies

Electronic search

The mentioned search was performed through electronic databases with search terms of ["kidney dysfunction" And "henna" Not "glucose-6-phosphate dehydrogenase (G6PD) deficiency"], ["henna" And "kidney"] in the present research.

Searching other resources

The author reviewed references of all included articles and performed hand searching of related journals to identify the additional relevant articles.

Study Selection

The search strategy was used to obtain titles and abstracts of articles that might be relevant to this review. The 5267 titles and abstracts were identified via electronic search in PMC, PubMed, Scopus, Embase, Google Scholar and hand searching by author. Total records of 5267 articles were identified and 5261 articles screened after deduplication. Of them, 5186 articles were excluded due to non-related subjects, review articles, others and 75 full-text articles were considered for eligibility. The 49 articles were excluded and then 26 published articles included in this research. Thirty patients with ["henna "And " kidney dysfunction" Not "G6PD-deficiency"], ["henna" And "kidney"] were enrolled for qualitative and quantitative synthesis.

Data collection and analysis

Data extraction and management

Data extraction was carried out by author and articles which reported in journals as non-English language were translated before assessment. There were no other languages in full-text articles in the present research. Where more than one publication of a article existed, reports were grouped together and the publication with the most complete data was included.

Data items

All patients with clinical, laboratory and radiologic presentations of henna usage and decreased estimated glomerular filtration rate (eGFR) or elevated (SCr) were considered in this research. Demographic and clinical features such as age, sex, different symptoms and physical signs were extracted from this study. Furthermore, biochemical variables of SCr, eGFR, serum total (CPK), serum CPK-MM, serum lactate dehydrogenase (LDH), serum electrolytes (calcium, phosphorus, magnesium, sodium, potassium), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, complete blood cell count (CBC), reticulocyte percent, direct and indirect coombs test, peripheral blood smear (PBS), urinalysis, urine eosinophils, urine hemoglobin, urine myoglobin and urine hemosiderin, urine electrophoresis, toxicological testing for PPD such as urine thin layer chromatography method (TLC) and thin layer chromatography-gas chromatography coupled with mass spectrometry (TLC-GC-MS), and blood levels of heavy metals (cadmium and lead) by graphite furnace atomic absorption spectrometry (GF AAS) were measured.

Definition

Kidney disturbance

AKI, AKD and CKD can form a continuum whereby initial kidney injury can lead to persistent injury eventually leading to CKD. AKI is

defined as an abrupt decrease in kidney function occurring over 7 days or less whereas CKD is defined by the persistent of kidney disease for a period of > 90 days. AKD is defined as acute or subacute damage and/or loss of kidney function for duration of between seven and 90 days after exposure to an AKI initiating event. Recovery from AKI within 48 h of the initiating event typically heralds rapid reversal of AKI that has been discussed in Acute Disease Quality Initiative 16 Workgroup (16th ADQI consensus report of 2017). Recent classification of kidney disease is according to cause, severity of structural and functional abnormalities, and duration of those abnormalities. With these criteria, it is classified to AKI, AKD, CKD and no kidney disease (NKD) that has been discussed in kidney disease: improving global outcomes [KDIGO] guidelines August 2020. CKD is classified zero to five stages (stages of 1, 2, 3a, 3b, 4 and 5) according to eGFR and kidney damage such as proteinuria (>200 mg/day or protein to creatinine ratio > 200 mg/g creatinine) or albuminuria (urinary albumin excretion ≥ 30 mg/day or albumin to creatinine ratio ≥ 30 mg/g creatinine). eGFR is measured through equations for estimation of creatinine clearance (CrCl), CockGroft-Gault equation, modification of diet in renal disease (MDRD) and chronic kidney disease-epidemiology collaboration (CKD-EPI) [9]. CrCl in 24-hr urine collection is expressed using urine creatinine (mg per deciliter or micromole per liter) multiplied in by urine volume (milliliter or liter) divided on plasma creatinine (milligram per deciliter or micromole per liter) multiplied in 1440 and its unit is expressed with milliliter per minutes (ml/min). Cockcroft-Gault equation is expressed as CrCl=(140-age)×wt divided on SCr×72, multiplication by 0.85 if female. MDRD equation given by: estimated GFR=175 × Standardized SCr $^{-1.154}$ × age $^{-0.203}$ × 1.212 [if black] × 0.742 [if female] where eGFR is expressed as ml/min/1.73m^2 of body surface area and SCr is expressed as mg per dl. The CKD-EPI equation, expressed as a single equation, is eGFR=141× min (Scr⁄κ,1) $^{\alpha}$ × max (Scr⁄κ,1) - 1.209 × 0.993^{age} × 1.018 [if female] - 1.159 [if black], where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and 0.411 for males, min indicates the minimum Scr⁄k or 1 and max indicates the maximum of Scr⁄κ or 1.

Biochemical variables

Serum creatinine in normal male adults is 0.8 to 1.3 mg/dl and in normal female adults is 0.6 to 1 mg/dl. Elevated serum creatinine is defined more than 1.3 mg/dl in male and more than 1 mg/dl in female sex. Serum creatinine in children is as follows: Cr=0.018+0.032 age. Serum creatinine in 1-20 years old male children is 0.35+ age in years/40 and in 1-20 years old female children is 0.35+ age/55. This value in edematous patients is expressed as creatinine production divided to 0.6*weight plus edematous weight. Creatine kinases (CK) are a dimer molecule and occur in three isoenzyme forms (MM, MB, BB). Serum total CPK in normal male adults is considered 51to 294 U/l and in normal female adults 39 to 238 U/l. Serum CK-MB in normal adults is defined 0-5.5 ng/ml and CK-MM3/MM1 value is < 1ng/ml. Serum LDH is defined 115-221 U/l. Seum calcium level is defined 8.6-10.3 mg/dl and serum phosphorus of 2.5-

4.5 mg/dl is considered as normal value. Serum magnesium is defined 1.6-2.3 mg/dl, serum Na level is defined 135-145 mEq/l and serum potassium is defined 3.5-5 mEq/l. Serum alanine aminotransferase (ALT) is defined 7- 41U/l and serum aspartate aminotransferase (AST) is 12-38 U/l. Serum total bilirubin is defined 0.3-1.3 mg/dl, direct bilirubin is defined 0.1-0.4 mg/dl and indirect bilirubin is defined 0.2-0.9 mg/dl. Reticulocyte percent in male adults is defined 0.8-2.3% and in female adults is defined 0.8-2% (corrected reticulocyte: 0.5-1.5%).

Toxicological testing for henna mixed with PPD

Toxicological testing for PPD poison detection includes urine thin layer chromatography method (TLC) and thin layer chromatography-gas chromatography coupled with mass spectrometry (TLC-GC-MS) in black stone analysis [10].

Assessment of risk of bias and quality in included articles

Case reports were analyzed using criteria developed by the Joanna Briggs Institute Critical Appraisal tool for case reports that has different assessment tools for each study design in question. The evaluation tool has 8 items for case reports.

Statistical analysis

Data were entered in Microsoft Excel 2010 software. Categorical variables are recorded as frequency (N) and percentage (%). The continuous variables were determined as to whether they were normally distributed using the kolmogorove-smirnov or shapiro-wilk test. Continuous variables with normal distribution reported as mean ± standard deviation (SD). Nonparametric variables are expressed as median and interquartile range (Q1, Q3 and IQR). Comparisons between continuous variables with normally distributed (ND) data assessed by two-tailed t test analysis. Effect size of intervention was assessed using Cohens' d test. Kaplan Meier analysis was used for survival probability. Significance was assessed with p-value of < 0.05.

Results

Description of studies

Results of the search and study selection

Author identified 5267 records after searching through electronic databases. After removing duplicated articles (N=6) and screening 5261 articles by titles/ abstracts, author discarded 5186 full-texts articles due to non-related subjects. Then 75 articles were eligible and 49 articles were discarded due to not non case reports. Of these, 26 published articles (30 case reports) were included and enrolled for participating in this study.

Included studies (criteria)

Thirty published articles (30 case reports or participants) were considered for inclusion in this research. All patients (participants) included in this systematic and meta-analysis study had kidney diseases in relation to henna consumption as topically or oral ingestion. These patients who had symptoms, signs, laboratory and imaging characteristics of henna dye-induced nephropathy and elevated serum creatinine levels or decreased eGFR were considered for this research. Toxicological tests for henna mixed PPD (henna powder, oral PPD in form

of liquid or powder) and laboratory analysis of henna stone or henna dye hair were performed in presence of availability.

Excluded studies (criteria)

Patients with henna consumption with kidney impairment at initial time or during follow up at time of article writing were discarded.

Risk of bias and quality in the included studies

Assessment of risk of bias and quality of included articles performed using Joanna Briggs Institute critical appraisal tools for case reports. Based on these criteria, four of thirty patients (4/30, 13.3%) earned eight score, twenty of thirty patients (20/30, 66.6%) attained to seven score, four of thirty patients (4/30, 13.3%) attained six score, two of thirty patients (2/30, 6.6%) attained to five score [Table S1].

Results of case studies

Patients' Characteristics

ىAmong screened 5261 full-text articles obtained in this research paper, 5186 articles were excluded due to unrelated subjects, review articles and other studies. Then 75 full-text articles were eligible and 49 articles were excluded due to non case reports (n=49). Finally 26 published articles were included in this study [11-36]. These 26 articles included 30 case reports that were examined 30 patients with clinical, laboratory and radiologic presentations of henna dye consumption and kidney impairment with and without toxicological testing were considered for qualitative and quantitative synthesis in this research [Fig. 2].

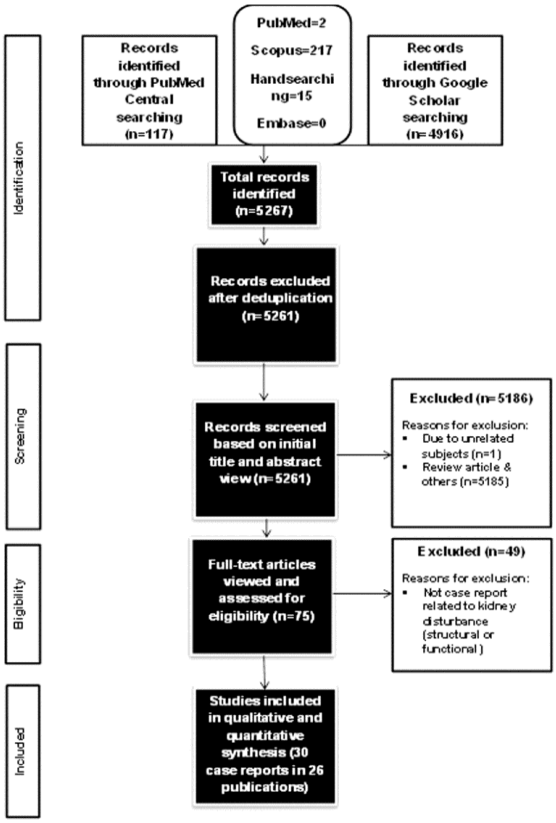

Fig. 2. Flowchart of current research.

In this research, thirteen of thirty patients belong to India country (13/30, 43.3%), four of thirty patients from Turkey (4/30, 13.3%), three of thirty patients from Sudan (3/30, 10%), two of thirty patients were from Iran, Egypt and Ireland (2/30, 6.6%) and one of thirty patients from other countries (1/30, 3.3%). The median age at time of diagnosis in henna-induced pigment nephropathy due to mixed henna was 23 years old (ranging from 3 days to 85 years old) and Q1 of 16, Q3 of 36 and IQR of 20 years old. Thirteen of thirty patients were male (13/30, 43.3%) and seventeen of thirty patients belong to female group (17/30, 56.6%). The mean average of age in male group was assessed 30.30±21.75 and in female group was assessed 27.47±16.05. There was not significant statistical significance in sex levels in henna-induced pigment nephropathy due to mixed henna (p-value=0.70) [Table S2].

Patients Complaints

The most common symptoms were assessed orofaciocervical swelling (8/30, 26.6%) and vomiting (7/30, 23. 3%) in this study. and Other symptoms include respiratory discomfort (5/30, 16.6%), abdominal pain, history of yellowish discoloration of sclera, history of decreased urinary output, history of urine discoloration (reddish, dark chocolate brown and darken-colored) [4/30, 13.3%], breathlessness, dizziness and shortness of breath (SOB) [3/30, 10%], myalgia, anorexia, nausea, dyspnea on exertion (DOE), bodyache, upper-lower lip swelling, feeling unwell and swallowing difficulty (2/30, 6.6%). In this context, seven of thirty patients (7/30, 23.3%) had history of topical henna usage, four of thirty patients (4/30, 13.3%) had history of henna powder ingestion, eighteen of thirty patients (18/30, 60%) gave history of oral PPD consumption in different forms in market, two of thirty patients (2/30, 6.6%) had history of topical mixed PPD with henna usage and one of thirty patient had history of inhalational hair-dye (1/30, 3.3%) [Table S3]. The most common sign in pigment nephropathy due to henna dye were abnormal general appearance (15/30, 50%), tachycardia (13/30, 43.3%), twelve of thirty patients had hypertension (12/30, 40%), eleven of thirty patients (11/30, 36.6%) had tachypnea, abnormal neurological exam, abnormal abdominal examination, abnormal lower extremity and abnormal skin (7/30, 23.3%), darken urine, facial edema (7/30, 23.3%), yellowish to yellowish-brown discoloration of sclera and skin, abnormal lung examination and swollen oral cavity (5/30, 16.6%), fever (4/30, 13.3%), pallor and abnormal joint exam (3/30, 10%), stridor and hypoxemia (3/30, 10%). Angioneurotic edema was seen in thirteen of thirty patients (13/30, 43.3%) and angioneurotic edema-like reactions was found in one of thirty patients (1/30, 3.3%). Psoriasis was seen in two of thirty patients (2/30, 6.6%) in the present research. Moreover, compartment syndrome were seen in two of thirty patients (2/30, 6.6%) that fasciotomy was recommended for two patients but performed in one of thirty patients (1/30, 3.3%) [Table S4].

Laboratory data

There was leukocytosis in seventeen of thirty patients (17/30, 56.6%) that quantitative measurement found in fifteen of thirty patients (15/30, 50%) with mean average of 22865.83±6876.6 cells/μl. Normal

leukocyte found in two of thirty patients (2/30, 6.6%) with mean average of 8600±1900 cells/µl. There was hyperleukocytosis in one of thirty patients (1/30, 3.3%) and leukopenia in one of thirty patients (1/30, 3.3%). Thrombocytopenia found in two of thirty patients (2/30, 6.6%) with the mean average of 78500±53500/µl and normal platelets detected in eight of thirty patients (8/30, 26.6%) with the mean average of 286875±73362.86/µl. Neutrophilia was found in seven of thirty patients (7/30, 23.3%) that quantitative neutrophilia was assessed in six of thirty patients (6/30, 20%) with the mean average of 89.16±2.47 %. There were anemia in seventeen of thirty patients (17/30, 56.6%) with the mean average of 9.22±2.86 g/dl and normal hemoglobin found in four of thirty patients (4/30, 13.3%) with the mean average of 12.22±0.617g/dl.

Corrected reticulocytosis found in three of thirty patients (3/30, 10%) with the mean average of 4.43±1.77% and reticulocyte percent (unmentioned correction) was found in three of thirty patients (3/30, 10%) with the mean average of 8.5±5.5%. Abnormal PBS was seen in seven of thirty patients (7/30, 23.3%). Toxic granulation infavor of sepsis found in one of thirty patients (1/30, 3.3%) and schistocyte detected in five of thirty patients (5/30, 6.8%). There was albuminuria in four of thirty patient (4/30, 13.3%), hematuria and proteinuria in three of thirty patients (2/30, 6.6%), pyuria and glycosuria in one of thirty patients (1/30, 3.3%) in urinalysis in the present research. Amorphous urate crystals, waxy and white blood cell (WBC) cast was seen in one of thirty patients (1/30, 3.3%) in urinalysis. There were proteinuria in four of thirty patients (4/30, 13.3%) that quantitative measurement was assessed in two of thirty patient (2/30, 6.6%) with the average mean of 3272.5 mg/24 hour. There was hypocalcemia in eight of thirty patients (8/30, 26.6%) that quantitative measurement was done in six of thirty patients (6/30, 20%) in this research. The mean average of hypocalcemia of this research was assessed 6.75±0.90 mg/dl. Hyperphosphatemia was seen in six of thirty of patients (6/30, 20%) that quantitative hyperphosphatemia was measured in four of thirty patients (4/30, 13.3%) with the mean average of 7.67±0.92 mg/dl. There was hyponatremia in three of thirty patients (3/30, 10%) with the mean average of 127±7.87 mEq/l. Hyperkalemia was seen in six of thirty of patients (6/30, 20%) with mean average of 6.44±0.61 mEq/l and hypokalemia was seen in one of thirty patients (1/30, 3.3%).

Hypoalbuminemia was found in four of thirty patients (3/30, 10%) with the mean average of 2.76±0.69 g/dl. Elevated erythrocyte sedimentation rate (ESR) was seen in two of thirty of patients (2/30, 6.6%) with the mean average of 73 ± 23 mm/hr in the present research. Elevated SCr was seen in twenty-two of thirty patients (22/30, 72.3%) with the mean average of 5.30±3.72 mg/dl. Elevated CPK was seen in seventeen of thirty patients (17/30, 56.6%) with the median of 22000 (Q1: 2780.5; Q3:96225.5; IQR: 93445; Min: 824; Max: 600000 and range of 599176 IU/l). Elevated uric acid was found in three of thirty patients (3/30, 10%) with the mean average of 8.53±0.77 mg/dl. Elevated LDH was seen in nine of thirty patients (9/30, 30%)

with the median of 3273 and IQR of 14453.5 (Q3:15500; Q1: 1046.5; Min:721; Max: 31500; Range: 30779) IU/l. Decreased bicarbonate ($HCO3^-$) was seen in nine of thirty patients (9/30, 30%) with the mean average of 18.33±3.75 mEq/l. Elevated total bilirubin was found in seven of thirty patients (7/30, 23.3%) with the mean average of 5.63±3.98 mg/dl and direct hyperbilirubinemia was seen in three of thirty patients (3/30, 10 %) with the mean average of 1.65±0.54 mg/dl. Indirect hyperbilirubinemia was found in one of thirty patients (1/30, 3.3%) in the present research. Elevated AST was seen in twenty-two of thirty patients (22/30, 73.3%) with median of 1262.5 IU/l, Q1 of 150 IU/l and Q3 of 3051IU/l and elevated ALT was seen in twenty of thirty patients (20/30, 66.6%) with the median of 725.5, Q1 of 141.5 IU/l and Q3 of 1597 IU/l in the present research. Corrected reticulocytosis was seen in three of thirty patients (3/30, 10 %) with the mean average of 4.43±1.77%. Reticulocytosis was seen in three of thirty patients (3/30, 10%) with the mean average of 8.26±4.5% in the present research. Urine test using TLC for PPD found in two of thirty patients (2/30, 66.6%) and TLC-GC/MS method detected possible PPD in urine of one patient out of thirty patients (1/30, 3.3%).

Pathology

There was ATN in three of thirty patients (3/30, 10%) and crescenric glomerulonephritis (GN) in one of thirty patients (1/30, 3.3%). Furthermore, pigment casts and chronic allograft nephropathy (CAN) found in one of thirty patients (1/30, 3.3%). Vasculitis was seen in one of thirty patients (1/30, 3.3%) in the present research [Table S5].

Imaging

There were normal chest x-ray in four of thirty patients (4/30, 13.3%) and abnormal chest x-ray found in two of thirty patients (2/30, 6.6%) in the present research. Renal ultrasonography was normal in four of thirty patients (4/30, 13.3%) and abnormal kidney imaging found in three of thirty patients (4/30, 13.3%). Ultrasound scan of kidneys in one of thirty patients (1/30, 3.3%) revealed bilateral bulky kidneys with loss of corticomedullary differentiation. Increased cortical echogenicity was seen in one of thirty patients (1/30, 3.3%). There was normal abdominal sonography in three of thirty patients (3/30, 10 %). Neck CT scan in one of thirty patients (1/30, 3.3%) showed extensive soft tissue swelling and edema with extension to the anterolateral of neck. Brain computed tomography (CT) scan performed in two of thirty patients (2/30, 6.6%) that showed subarachnoid hemorrhage in one of thirty patients (1/30, 3.3%) and another patient showed diffuse cerebral edema and intracranial hemorrhage in right parietal lobe. Abdominal CT scan performed in one of thirty patients (1/30, 3.3%) with characteristics of free fluid collection in the perihepatic and perisplenic recesses, fatty liver, inflammation and edema of the cutaneous and subcutaneous tissues [Table S6].

Treatment

Hemodialysis (HD) performed in thirteen of thirty patients (13/30, 43.3%) and peritoneal dialysis (PD) was performed in three of thirty patients (3/30, 10 %). Continuous arteriovenous hemofiltration (CAVH), continuous venovenous hemodiafiltration (CVVHDF), continuous renal replacement therapy (CRRT) and extracorporeal

membrane oxygenation (ECMO) were done in one of thirty patients (1/30, 3.3%) in the present research. Hydration was mentioned in thirteen of thirty patients (13/30, 43.3%) and oxygen was mentioned in eight of thirty patients (8/30, 26.6%). Gastric decontamination or gastric lavage was performed in four of thirty patients (4/30, 13.3%) and forced diuresis was done in seven of thirty patients (7/30, 23.3%). Urine alkalization was done in eleven of thirty patients (11/30, 36.6%) and bicarbonate therapy was performed in nine of thirty patients (9/30, 30%). Furosemide therapy performed in eight of thirty patients (8/30, 26.6%). Steroid therapy has been performed to various methods and are as follows: dexamethasone in five of thirty patients (5/30, 16.6%), prednisolon in two of thirty patients (2/30, 6.6%), pulse dose of methylprednisolone in two of thirty patients (2/30,6.6%), intravenous (IV) hydrocortisone in seven of thirty patients (7/30, 23.3%), solumedrol in one of thirty patients (1/30, 3.3%) and unmentioned steroids in three of thirty patients (3/30, 10%). Packed red blood cell (PRBC) was performed in five of thirty patients (5/30, 16.6%). Antibiotic therapy was given in four of thirty patients (4/30, 13.3%) and antibiotics such as ceftriaxone, vancomycin, cefepime and fluxacillin was seen in one of thirty patients (1/30, 3.3%) in the present research. Tracheostomy performed in six of thirty patients (6/30, 20%) and intensive care unit (ICU) admission found in five of thirty patients (5/30, 16.6%). Endotracheal intubation was performed in ten of thirty patients (10/30, 10%). Seven of thirty patients underwent ventilator (7/30, 23.3%). Antihistamines were used in four of thirty patients (4/30, 13.3%). Ranitidine was used in three of thirty patients (3/30, 10%). Adrenalin was used in two of thirty patients (2/30, 6.6%). Fresh frozen plasma (FFP) and plasma exchange was used in two of thirty patients (2/30, 6.6%). Oral calcium was seen in two of thirty patients (2/30, 6.6%) in current research [Table S7].

Outcomes and Follow UP

In follow up of these patients, twenty of thirty patients (20/30, 65.51%) developed clinical recovery and three of thirty patients (3/30, 10%) found deterioration. One of thirty patients (1/30, 3.3%) had neurological sequella and another patient developed hypotension (1/30, 3.3%). Five of thirty patients (5/30, 16.6%) stayed on HD that two of thirty patients discontinued HD (2/30, 6.6%). Fifteen of thirty patients (15/30, 50%) discharged. There was adequate urinary output in seven of thirty patients (7/30, 23.3%) in the current research. Blood urea nitrogen (BUN) was checked in seven of thirty patients (7/30, 23.3%) that quantitative measurement was done in three of thirty patients (3/30, 10%) while elevated Bun was seen in two of thirty patients (2/30, 6.6%) with the mean average of 109.67±20.27 mg/dl. Bun was normal in five of thirty patients (5/30, 16.6%) in the present research. Elevated urea was seen in three of thirty patients (3/30, 10%) with the mean average of 170.36±80.93 mg/dl. Elevated serum creatinine found in three of thirty patients (3/30, 10%) with the mean average of 8.01±0.772 mg/dl. Elevated Bun was seen in two of thirty patients (2/30, 6.6%) with the mean average of 109.67±20 mg/dl.

Elevated AST was seen in four of thirty patients (4/30, 13.3%) with the

mean average of 1293.25±1708.09 U/l and elevated ALT was observed in four of thirty patients (4/30, 13.3%) with median of 135 and range of 1922 U/l. Elevated total bilirubin was seen in three of thirty patients (3/30, 10%) with the mean average of 2.66±1.38 mg/dl and direct hyperbilirubinemia was seen in two of thirty patients (2/30, 6.6%) with the mean average of 1.97± 0.98 mg/dl. Elevated CPK was seen in four of thirty patients (4/30, 13.3%) with the mean average of 11267.5±12215.82 IU/l.

Primary end-points

AKI and AKD are of outcomes of primary end-points of henna-induced pigment nephropathy. Three of thirty patients (3/30, 10%) developed AKI and one of thirty patients (1/30, 3.3%) found AKD during follow up in the present research. Three of thirty patients (3/30, 10%) developed persistent kidney failure with kidney replacement therapy. Twenty of thirty patients (20/30, 66.6%) found clinical recovery. Nine of thirty patients (9/30, 30%) died that five of thirty patients (5/30, 16.6%) were expired due to cardiac arrest, two of thirty patients (2/30, 6.6%) succumbed due to infection (bronchopneumonia and hospital-acquired pneumonia) and cause of death in two of thirty (2/30, 66.6%) patients was unknown. Six of nine dead patients were female (6/9, 66.6%) and three of them belong to male group (3/9, 33.3%). Patients used topical/inhalational henna in nine out of thirty patients (9/30, 30%) and twenty-one out of thirty patients consumed oral mixed henna (21/30, 70%) in this research. Proportion of mortality in patients with topical henna versus (vs.) oral mixed henna was assessed 44.4% (4/9) vs. 23.8% (5/21) in current research. There was inadequate data for time of death in three of thirty patients and mortality analysis performed in twenty-seven of thirty patients. Comparison between values (2/6 vs. 5/21) revealed that death probability in patients with ingested vs. topical mixed henna usage was not significant statistically using Kaplan Meyer analysis (p-value: 0.51). Mortality probability of topical vs. ingested mixed henna has been depicted in Fig. 3 [Table S8].

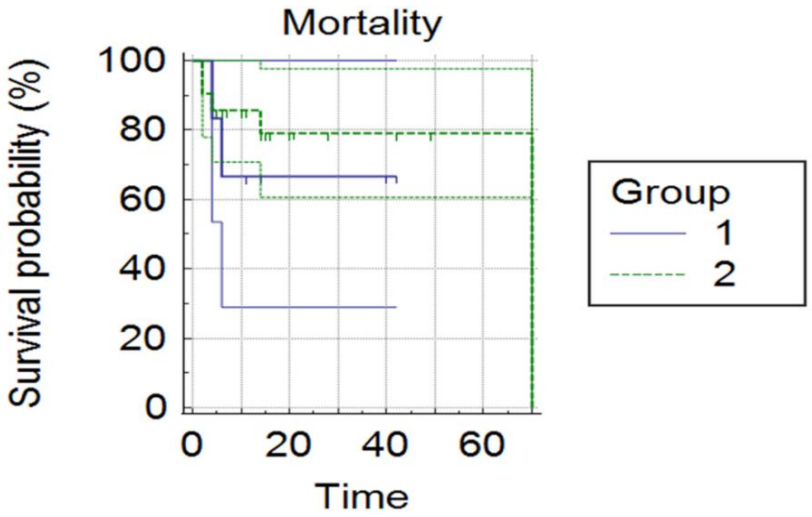

Fig.3.Kaplan miere curve of mortality probability of topical mixed henna versus ingested mixed henna in the current research.

Effect size of elevated SCr based on the last serum creatinine measurement or the last serum creatinine measurement on dialysis modalities using standardized mean difference by cohen's-d law was assessed 1.637 (large effect).

Secondary end-points

There was elevated serum CPK in one of thirty patients (1/30, 2.9%) during follow up. The mean average of elevated SCr in pre-HD and post-HD were assessed 7.04±4.90 and 4.59±3.06 mg/dl, respectively. Comparison between two variables using paired t test was assessed with *p*-value of 0.37 (not significant) [Table S9].

Discussion

The combination of henna with PPD, known as black henna, is used for cosmetic indications is highly toxic. It is applied as temporary tattoo to decorate hands and feet. This status causes multisystem toxicity and high mortality in patients with severe toxicity. Systemic intoxication presents as angioneurotic edema, hepatotoxicity, rhabdomyolysis and acute renal failure. The characteristic triad of PPD poisoning include early angioneurotic edema of face and neck with stridor, rhabdomyolysis with chocolate colored urine and acute renal failure can be confirmative in lack of laboratories methods and absence of symptoms. The major product of PPD is Bandrowski's base is formed by the oxidation reaction of PPD with base in an alkaline which is allergen, mutagenic and highly toxic. As previously mentioned, prevalence of this nephropathy was higher in female group in the current research that was in agreement with study by Shigidi *et al* [37]. The female to male ratio in our study was assessed 1.3 and the median age of patients was 23 years but this ratio in study by Abbas *et al* was reported 24/1 and range of age was 20-30 years old [38]. Seventy percent of patients found clinical recovery and thirty percent of them developed mortality. These values are different with study by Naqvi *et al* that clinical recovery and mortality in that research were 77 and 16%, respectively [39]. Nephrotoxicity is one of dangerous complications of henna-induced pigment nephropathy as frequency of acute renal failure (ARF) in our study was assessed 20% while this value in study by Arif *et al* was low. Acute renal failure observed in 65 patients (81.25%) that 60 patients (92.31%) found clinical recovery with treatment and 5 patients (7.69%) developed residual kidney damage [6]. Moreover, studies in Sudan country indicates that henna tattoo (drugs and intoxications) is known as third cause of AKI. Another point that must be considered, is presence of high mortality rate (9/30, 30%) in patients with mixed henna pigment nephropathy while study by Shigidi *et al* reported mortality rate of 3.3% (1/30). In another study by Shaikh *et al*, mortality rate was assessed 34.61% (78/130) [40]. In this context, Study by Yousif *et al* revealed that henna dye was accounted for 5.6% (4/71) of AKI etiologies [41]. Therapeutic modalities in this nephropathy consist rinsing of oral cavity with water and ingesting milk for alleviating the symptoms. Gastric lavage with 2% sodium bicarbonate is also effective. Due to low molecular weight and hydrophilic nature, PPD has low absorbability on activated charcoal. Mild respiratory distress may respond to chlorpheniramine [36]. ARF of

henna-induced pigment nephropathy is due to urine myoglobin and methemoglobin that culminate in to dialysis modalities. There is controversy about efficiency of dialysis modalities in toxic removal because PPD itself is not dialyzable compound and dialysis modalities in this disease are used as supportive measure in mixed-henna dye poisoning for myoglobin and methemoglobin removal in urine. Hemoperfusion and hemodialysis trials in PPD removal have been tried and were associated with variable results [42]. In the present research, effect of mixed henna on kidney outcome was assessed large effect that needs to special attention. Therefore, it is essential to implement awareness about interventions to curtail the misuse of hair dyes and restrict the sale of hair dyes with high PPD concentrations [43]. Limitations of this study were insufficient and inadequate data on medical records and there was little information about diagnostic methods of PPD on literature review on scientific databases.

Conclusion

Effect of mixed henna on kidney outcome was assessed large in this research. Because mixed henna is a non-dialyzable compound and contains dangerous complications, it is necessary that its consumption be avoided. Hence stopping mixed henna sale is an important recommendation that must be noticed.

Ethics Approval and consent to participate

Authors of published articles stated that research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. They described that subjects (or their parents or guardians) were given their informed consent and study protocol was approved by the institute's committee on human research.

Availability of data and material

Author requested that the datasets be located in Figshare repository.

Competing interests

The author (s) declares that they have no competing interests**.**

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Table S1. The Joanna Briggs Institute Critical Appraisal for assessment of case reports in included articles.

Item / Author	Demographic characteristics described	Subject history described	Pre-intervention clinical condition described	Diagnostic tests or assessment methods and result	Intervention/ treatment described	Post-intervention clinical condition described	Adverse events	Takeaway lesson	TS
Gowda	Y	Y	Y	UC	UC	Y	UC	Y	5/8
Brown 1	Y	UC	UC	Y	Y	Y	Y	Y	6/8
Brown 2	Y	UC	UC	Y	Y	Y	UC	Y	5/8
Khine	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Singla	Y	Y	Y	Y	UC	Y	UC	Y	6/8
Qurashi	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Minoo	Y	Y	Y	Y	Y	UC	UC	Y	6/8
Asgari	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Kaballo	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Chaudran	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Beshir	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Handyal	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Sampathkumar1	Y	Y	Y	Y	Y	UC	UC	Y	7/8
Sampathkumar2	Y	Y	Y	Y	Y	UC	UC	Y	6/8
Khatua1	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Khatua2	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Khatua3	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Jain	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Narang	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Amira	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Mendonca	Y	Y	Y	Y	Y	Y	UC	Y	7/8
AKl	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Katar	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Oner	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Anuradha	Y	Y	Y	Y	Y	Y	UC	Y	7/8

Shalaby	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Soker	Y	Y	Y	Y	Y	Y	UC	Y	7/8
Kheir	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Sik	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Prabakaran	Y	Y	Y	Y	Y	Y	UC	Y	7/8

Table S2a. Demographic characteristics of patients with henna-induced pigment nephropathy.

Country	Assessment	Diagnosis	Relative	Ethnicity	Parents	Family history	Center	Sex	Age	Case report
USA		angioedema					ED	male	59 y/o	Gowda
Ireland		CRF					hospital	female	51 y/o	Brown 1
Ireland							hospital	female	62 y/o	Brown 2
Myanmar		AKI				mother	hospital	Man	34y/o	Khine
India		ARF, rhabdomyolysis					ER	male	20 y/o	Singla
Saudi Arab	excellent						ER	male	32 y/o	Qurashi
Iran		AKI, Single kidney					hospital	female	62 y/o	Minoo
Iran		DIIHA					ER	man	85 y/o	Asgari
Sudan		Angioneurotic edema		Sudanese			ER in hospital	Male	36 y/o	Kaballo
India		Rhabdomyolysis					hospital	female	13 y/o	Chandran
Sudan		ATN		Sudanese		suicide with same	hospital	female	14 y/o	Beshir
India							ER	female	15 y/o	Handyal
India		ARF, RML, LI					hospital	female	23 y/o	sampathkumar 1
India		ARF, RML, LI					hospital	female	19y/o	sampathkumar 2
India		AKI					hospital	female	36y/o	Khatua
India							ER	female	18y/o	Khatua
India							hospital	female	23y/o	Khatua
India		AKI					ER	male	23y/o	Jain

India	ATN	ICU	female	19y/o	Narang
Tunisia	ARF	ER & ICU	female	33y/o	Amira
India		hospital	female	22y/o	Mendonca
Egypt	ARF, IN, pneumonitis, bronchitis	Pediatric ER	female	32y/o	Akl
Turkey	Renal Failure	ER	male	3 days/0.008	Katar
Turkey		EC	female	16y/o	Oner
India		ED	male	22y/o	Anuradha
Egypt		hospital	male	42y/o	Shalaby
Turkey		PD	boy	11y/o	Soker
Sudan	acute hemolysis	hospital	boy	6y/o	Kheir
Turkey		hospital	female	9y/o	Sik
India		hospital	man	24 y/o	Prabakaran

ARF, acute renal failure; AKI, acute kidney injury; ATN, acute tubular necrosis; CRF, chronic renal failure; DIIHA, drug-induced immune hemolytic anemia; EC, emergency clinic; ED, emergency department; ER, emergency room; ICU, intensive care unit; IN, interstitial nephritis; LI, liver injury; PD, pediatric department; RML, rhabdomyolysis.

Table S2b. Continued.

	Country	Number	Male	Female
	India	13	59	51
	Ireland	2	34	62
	Sudan	3	20	62
	Myanmar	1	32	13
	Tunisia	1	85	14
	Egypt	2	36	15
	Iran	2	23	23
	Saudi Arab	1	0.008	19

				Turkey	4	22		36
				USA	1	42		18
						11		23
			28.86			6		19
			SD:19.09			24		33
								22
						Mean:30.30		32
						SD: 21.75		16
								9
		t-Test: Two-Sample Assuming Unequal Variances				ND	NND	
								22
Variable 2	*Variable 1*			Overall age			Q1=1.5	
27.47059	30.30831	Mean		Median:23			Q3=4.5	
274.0147	512.5237	Variance		Mean age:28.8±18.79			Q2=3	
17	13	Observations		Q1=16			IQR=3	
	0	Hypothesized Mean Difference		Q2=23, Q3=36,IQR=20			SD=16.05	
	21	df						
	0.380762	t Stat						
	0.353602	P(T<=t) one-tail						
	1.720743	t Critical one-tail						
	0.707205	P(T<=t) two-tail						
	2.079614	t Critical two-tail						

Table S3a. Symptoms of patients with henna-induced pigment nephropathy.

Extremity	IL	GI	Weakness	Angioedema	Vomiting	Swelling	Oral PPD	Abdominal pain	Conjunctiva	Urine History	Topical henna	Myalgia	Time	Decreased U.OP	Pallor	Symptom

													Case Report
			AE-like reaction		Asymmetric facial						6 days		Gowda
									henna hair dye	+	4 years later		Brown 1
									henna hair dye		3 wks	oliguria	Brown 2
			+				yellowish	dark-color			7 wks		Khine
				+		black powder	pain	yellowish	dark-color		10 days	decreased	Singla
											6 wks		Qurashi
			+		face				henna powder		2 months	+	Minoo
							pain				2 wks		Asgari
			+								3 wks later		Kaballo
						superv asmol 33					16 days		Chaudran
				+	orofacial	hair dye tancho	Severe RUQ				15 days		Beshir
			+			superv asmol					6 days		Handyal

				superv asmol33						2 days		Samputhkumar 1	
				superv asmol33						7 days		Samputhkumar 2	
	+			supper vasmol 33						15 days		Khatua	
	+			superv asmol33						4 days		Khatua	
	+			superv asmol33						15 days		Khatua	
	+			hair dye ingestion						5 days		Jain	
	+	recurrent	face, tongue, neck	hair dye ingestion			DCB			20 days	decreased	Narang	
		+		black stone		discoloration			+	1 wk		Amira	
	+			superv as33						10 wks		Mendonca	
		+			Epigastric pain					2 wk		Akl	
								topical henna		40 days		Katar	
	+		diffuse orbital,	mixed PPD						11 days		Oner	

						neck , face										
			+	recurrent		tongue, face, neck	20 gr by father						2 days			Anuradha
			+			facial, laryngeal edema	PPD						17 days			Shalaby
		+									reddish	henna-whole hands+ feet	11 days	+		Soker
									yellowish			Black hair (skin, hair)	6 wks			Kheir
				+									4 days			Sik
Pain & stiff	+	+				facial	PPD pellets						6 days			Prabhakaran
					7	vomiting		lethargy	1	hx of cyanosis	1					
					8	Orofacial & neck		loss of appetite	1	headache	1					
					4	abdominal pain		wt loss	1	feeling unwell	1					
					4	oliguria		giddiness	1	somlonence	1					
					4	urine discoloration		feeling unwell	2	constipation	1					
					2	myalgia		seizure	1	distention	1					

4	yellowish	generalized fatigability	1	dependent edema	1
3	dizziness	abdominal bloating	1	impairement of cons	1
5	Respiratory discomfort	unidentified toxic	1	four limbs pain	1
3	breathlessness	fingers staining	1	feeling unwell	2
1	Pallor history	altered sensorium	1	Gene itching	1
2	anorexia	stridor	1	Inter lacrimation	1
2	nausea	laryngospasm	1	Pain & stiffness in extremity	1
2	DOE	oropharyngeal pain	1		
2	bodyache	thoracic pain	1		
2	swallowing difficulty	difficulty speaking	1		

2	upper-lower lip swelling	paresthesia	1
1	History of fever	joint swelling	1
1	weakness	difficulty breath	1
3	SOB	LDD	1

AE, angioedema; DCB, dark chocolate brown colored; DOE, dyspnea on exertion; GI, gastrointestinal itching; IL, intermittent lacrimation; LDD, lower disability; PPD, para-phenylenediamine; RUQ, right upper quadrant; SOB, shortness of breath; U.OP, urinary output; Wk, week. Positive mark indicates presence of symptom.

Table S3b. Continued.

Table S3c. Continued.

Laryngospasm	Stridor	Altered sensorium	Cervicofacial edema	Suicide	Toxic agent	Respir distress	Staining fingers	IBS	Abdominal bloating	General fatigability	Seizure	Giddiness	Alcohol
													+
									+	+	+	+	
								+					
						+	+						

				2 older siblings							
		+									
+		+			+						
					+						
				+							200 ml
					+						
				unknown							
				attempt							
					+						
				+							
				+							

Table S3d. Continued.

Atrial Flutter-post ablation	**Paresthesia**	**Four limbs**	**Past CVA**	**Fresh packet**	**Difficulty in speaking**	**SOB**	**Throat pain**	**Breathlessness**	**Difficulty in swallowing**	**Bodyache**	**Oropharynx**
+											

				+					
				+					
									pain
					+	+	+	+	
					+	+	+		
	four limb pain	+	+	+				generalize d	
+									
						+			
	four limb pain								
				+					

Table S3e. Continued.

IOC	Feeling unwell	Circumcision	Headache	Unidentified substance	Cyanosis	Derma consultation	upper-low lip	difficulty in breath	Hx of allergic contact dermatitis	Erythematous rash	Burning	Depression	OA
						not PPD patch	+	+	+	+	+	+	+
	+												

			+		+										
				oral	+										
		henna applied													
		henna applied													
+	+														

Table S4a. Signs of patients with henna-induced pigment nephropathy.

Neck	Generalized Appearance	Neurologic Exam	Abdomen	Urine color	Icterus	Height	Weight	O2 saturation	Blood Pressure	Respiratory Rate	Heart Rate	Pallor	Temprature	Sign
Erythematous rash									hypertensive	nl	nl		107 F	Gowda
	obese puffy								normotension				38.8 oC	Brown 1 Brown 2
	unwell	dizzy			+				150/90		100	+	37.8 oC	Khine
	inebriated, anxious			black-color					110/70	20	102		afebrile	Singla
	ill-looking, fully Conscious, oriented		soft, distension, tympanic	dark black	deeply-sclera			83%	169/110		98		37oC	Qurashi

							130/80		86		Minoo
		restless	periumbilical ten		sclera	78	150/70	32	100		Asgari
		nl	nl				170/90	24	100		Kaballo
	intubated						80/30		180		Chaudran
		alert	tenderness				110/70	18	98		Beshir
	RD	semi consciousness, restless					140/94	36	130		Handyal samputhkumar samputhkumar
	dyspnea	nl	nl, ascites	dark			150/90	32	80		Khatua
	dyspneic										Khatua
							120/70		80		Khatua3
			mild epi ten			98	110/80		108		Jain
					deep jaundice		140/90	26	48		Narang
		conscious		black				eupneic			Amira Mendonca
		critical illness, neurologic					90/60				
	breath discomfort		epigastric tender				110/70		100		Akl
	RD	decreased spontaneous activity				2600 gram	63/36		128		Katar
swollen	RD, agitation, cyanosis					85%	160/95	35	130		Oner
	cons, oriented			dark-chocolate-			130/86	30	104		Anuradha

					brown									
	dyspenic,alert							120/80	18	80		37oC	Shalaby	
					reddish-color			80/60		120	+	36.5 oC	Soker	
	pale, slight jaundice	irritable					99%	100/70	30	125	+	37.3 oC	Kheir	
	poor, slow breath	impaired LOC	liver:3cm BCM					72/33	28	80, weak			Sik	
					chocolated			190/110					Peabahakaran	

BCM, below costal of margin; F, Fahrenheit; Ht, height; LOC, level of consciousness; nl, normal; RD, respiratory distress; Wt, weight. Positive sign indicates presence of symptom.

Table S4b. continued.

Internal Foley catheter	**facial edema**	**Eye**	**calve muscle**	**JVP**	**Peri vascular**	**CV system**	**Bottle black powder**	**Joint/exam**	**Wide pp**	**Lung**	**Skin**	**Lower extremity**	**Sensory**
											bullous		
													intact
								2 nodular on lt elbow		lt basal consolidation		legs edema	
							PPD						
						normal				normal	henna staining hands &foot		
								nodular lesion	150/70	gene wheezing			

			tender …	raised	LE impalpable	nl auscultation					swollen, very tense, tender
+	+	chemosis				$S3^{+}$gallope					
						nl		normal			
	swelling Facial&Neck& Mouth					nl		edema of chest			
								no abnormality			
	+					nl		nl			pedal edema
	+										tender
									papules		
											flaccid quadriplegia
								scattered wheezing			
				10 cm H2O		Right ventricular heave			orange		orange
	+										
	+										tender
								scatter rales			
									psoriatic		

		gallope, SSm		hand+foot henna edematous, erythematous plaque	
			elbow/knee		
Facial puffiness					Swelling feet

Table S4c. Continued.

skin color	limbs	Muscle exam	Compartment Syndrome	Bedside larynx	Upper extremity	laryngeal edema	stridor	tetany	oral cavity	crepitation chest	GCS
			+	nl, then abnormal	erythematous rash						
											15
										+	
								+	conges, full		
									conges, full		
							+		swollen		
							inspiratory				13
						+			dry black tongue		
		hypotonia									
	stiffness				tender		inspiratory		swelling tongue		

			generalized tenderness												
		extensor surfactant													
yellow-brown															
		bilateral PP edema													

Table S5a. Laboratory findings of patients with henna-induced pigment nephropathy.

CPK	LDH	U/A	K	Na	SCr	Bun	cRC	PBS	PMN	Plt	WBC	Hb	U.OP	Laboratory data
>22000 U/l			hyperkalemia								16500			Gowda
					7.7 mg/dl							8.6		Brown 1
			hyperkalemia		9.5 mg/dl							10.7		Brown 2
	1925.4	darked color	4.5	131	1015 micro					25000	35.59	3.3	anuria	Khine
> 40000	9000	Alb:3+, RBC:2-4	3.8	135	0.7 mg/dl					280000	12800	13		Singla
			4.7	139	138 micro	14.9 mmol/l				388000	27400	11.2		Qurashi

					6.7 mg/dl						7.7		Minoo
	3273	4+proteinuria	5.93	135	1.13 mg/dl	schistocyte			285000	36000	9.5		Asgari
50130		brownish	4.2	116	12 mg/dl					22300	12	anuria	Kaballo
52834			3.3	144	1.6 mg/dl		92%		211000	2.26			Chaudran
		Hb, waxy, WBC cast			70 micro								Beshir
3420	995				1.5 mg/dl					17000	8.6		Handyal
172825			6.3		3.8 mg/dl						11.6		sampathkumar
121851			4.1		5.5 mg/dl						10.6		sampathkumar
					9.5 mg/dl		89%			18600	11.8	<100 ml	Khatu1
	31500	Hematuria + proteinuria			1 mg/dl		86%			24200	10.6	< 50	Katua2
16440					0.96 mg/dl		90%			10500	10		Khatu3
1230		darked urine			3.8 mg/dl							decreased	Jain
21470		urine albumin:3+	4	149	1 mg/dl	2%		86/L9/M5	280000	22500	12.3	350	Nanrang
600000	15000	black	hyperkalemia		297 micr/l				562000	hyperleukocytosis			Amira
70600		blackish	7.2, nl		5.8 mg/dl	toxic granulation		prominent polymorphous		22600	13.2	oliguria,anuria	Mendonca

		amorphous urate		nl	6.4, 7.4	38.5 mg/dl					leukocytosis	10	nl	Akl
1453 U/l			5.7		1.7 mg/dl 0.9, 7.8 mg/dl			hemolysis		132 000	18900	13 .5	decreased	Katar Oner
296000	16000		7.1	13 4	3.8 mg/dl			anisopoikilocytosis, fragmented RBC	92/8	150 000	20000	9	50 ml -16 hr	Anudhara
3965			4		6.3 mg/dl	176 mg/dl								Shalaby
254	721				0.8 mg/dl	90 mg/dl	6.2 0%	anisocytosis, poikilocytosis	P70/L6%/M4	342 000	6700	4. 5		Soker
		few puss, bilirubin:++	4.2	13 6	0.5 mg/dl		5.1 0%	anisocytosis, hypochromic , nucleated RBC		359 200	18200	4		Kheir
2141		coffee-colored			1.13 mg/dl						34500		<0.5 ml/kg/hr	Sik
824	1098		hyperkalemia		12.4 mg/dl			schistocyte, IVH					anuria	Prabahakaran

Bun, blood urea nitrogen; CPK, creatine phosphokinase; cRC, corrected reticulocyte percent; Hb, hemoglobin; IVH, intravascular hemolysis; K, potassium; LDH, lactate dehydrogenase; Na, sodium; PBS, peripheral blood smear; Plt, platelet; PMN, polymorphonuclear neutrophils; RBC, red blood cell; UA, urinalysis; U.OP, urinary output; WBC, white blood cell count.

Table S5b. Continued.

Reticulocyte	IgM for HEV	Malaria test	D&I coombs	PT	Urea	Alkaline phosphatase	AST	ALT	Indirect. Bilirubin	Direct bilirubin	Serum total bilirubin	Eosinophil	lymphocyte
					32 mmol/l								
					61 mmol/l								
					46 mg/dl	nl	83	nl			50 micro/l		
					29 mg/dl						0.6 mg/dl		
				12.7			114	120	73	27 micromol/l	202 micromol/l		
							261	2490	1280				
				14.7	94 mg/dl		293	78	52	1.02 mg/dl	9.93 mg/dl		
					195 mg/dl			150	115		0.7mg/dl		
						nl		2529	424		37.6 micro/l		
								350	290				
								188	168				
					87 mg/dl			1501	1633				
					132 mg/dl			3051	596				
					187 mg/dl		64	1175	1335		0.5 mg/dl		
					23 mg/dl		28	6400	2170		0.7 mg/dl		

				54 mg/dl	103	1734	855			0.84 mg/dl
				100 mg/dl						
				15 mg/dl	41	566	420		0.43mg/dl	
				10 mmol/l		10500	156 1			
				105 mg/dl		5800	320 0			nl
14%			45	154 mg/dl		139	20			
						1350	165 7			
3%		-	nl	120 mg/dl		84	104			1.1 mg/dl
						4420	105 5			
						420	104	5.2 mg/dl		
	-	-		75 mg/dl					5.13 micromol/l	51.3 micromol/l
				40 mg/dl		8755 U/l	455 7		2.36 mg/dl	8.63 mg/dl
7.8%				210 mg/dl						

Table S5c. Continued.

PCO2	pH	Amylase	RDW	MCHC	MCH	MCV	ESR	Renal Bx	Biopsy skin	urine protein	CrCl	vitamin D	Troponin T
								crescentric GN	allergic vasculitis	6 gram in 24 hr	11 ml/min	6.16 ng/ml	
32.9	7.42	33					96			545 mg			
38.7	7.4	45	18.8	32.65	31.25	95.72	50	ATN					
5.7 Kpa=42.7	7.41												2389 pg/ml
								ATN					
	6.98												
23	7.46												
29	7.36												
										proteinuria			
													0.3 ng/ml
								CAN,ATN, pigment		proteinuria			

			71		7.1									
				partial MA										
			33		7.3									
			36		7.14									
				MA								+		

ATN, acute tubular necrosis; Bx, biopsy; CAN, chronic allograft nephropathy; CrCl, creatinine clearance; ESR, erythrocyte sedimentation rate; GN, glomerulonephritis; MA, metabolic acidosis; MCV, mean corcospular (or cell) volume; MCH, mean corpuscular (or cell) hemoglobin ; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

Table S5d. Continued.

HCO3	Chloride	Globulin	Albumin	G6PD deficient	Urine toxicology	UT	INR	PTT	Blood sugar	Vitamin B12	folic acid	ferritin	CRP
20	84.7	22.4	30.1	nl					121				
22.5			39					31.8	4.5				
				12 unit/g	morphine	1+ glycosuria	1.17	31	200	548	13.3	< 2000	139.6
		2.9	3.5										
26			43 g/l			2-4/HPF; +heme							
14			1.8										
16			3.4										

16.1												
				chocolate brown								
				myoglobin								
								76				
18, 15												31.5 mg/dl
24			nl			6.08	145					0.4 g/dl
				chocolate brown								
18.3							nl	108				
				dark brown								
			Brewerin, -deficient	1+P, 3+bili tea-like								
14						4.3		24				
MA												

CRP, C-reactive protein; G6PD, glucose-6-phosphate dehydrogenase; HPF, high power field; INR, international normalized ratio; MA, metabolic acidosis; PTT, partial thromboplastin time; nl, normal; UT, Urine test.

Table S5f. Continued.

MetHb	Serum lactate	CPK-MB	Hct	IF of biopsy	urine test (TLC)	uric acid	granular cast	RBC in urine	WBC in urine	Albuminuria	Urine PE	Serum PE
										3+		

		8500 U/l									-	-
				-	PPD	9.5	4+	uncountable	uncountable	3+		
1%	2.2 mmol/l	500 ng/ml	41.70 %									
					PPD							
	74 mg/100											
						7.6						
						8.5						
											myoglobin	
						3.9						
	11 mmol/l											
			13.10 %									
15 mmol/l												

Hct, hematocrit; CPK-MB, creatine phosphokinase-MB; IF, immunofluorescence; MetHb, methemoglobin; PE, protein electrophoresis; PPD, para-phenylenediamine; RBC, red blood cell; TLC, thin layer chromatography; WBC, white blood cell.

Table S5l. Continued.

Direct Bilirubin	HCO3	CPK	LDH	Hypokalemia	K	Serum Na	SCr (mg/dl)
1.57	20	22000	1925.4	3.3	5.9	131	7.7
1.02	22.5	40000	9000		6.3	116	9.5
2.36	26	50130	3273		7.2	134	11.46
	14	52834	995		5.7		1.55
	16	3420	31500		7.1		6.7
	16.1	172825	15000				12
	18	121851	16000				1.6
	18.3	16440	721				1.5
	14	1230	1098				3.8
		21470					5.5
		600000					9.5
		70600					3.8
		1453					3.35
		296000					5.8
		3965					6.4
		2141					1.7
		824					3.8
							6.3
							0.8
							0.5
							1.13

	ND	NDD	NDD	ND	M:127	ND
Mean=1.65	18.33	Q1:2780.5	Q1:1046.5	M:6.44	SD:7.87	M:4.97
SD:0.54	3.75	Q2:22000	Q2:3273	SD:0.61		SD:3.46
		Q3:96225.5	Q3:15500			
		IQR:93445	IQR: 14453.5			
		Min:824	Min:721			
		Max:600000	Max:31500			
		Range:599176	Range: 30779			

Table S5m. Continued.

cRetic	Ca	Pi	ESR	S albumin	uric acid	AST	ALT	T.bili	Indirect
2	5.6	9.1	96	3.1	9.5	83	73	2.92	5.2 mg/dl
6.2	7.3	6.5	50	1.8	7.6	120	1280	11.71	
5.1	7.3	7.6		3.4	8.5	2490	52	9.93	
	6.1	7.5				78	115	1.1	
	8.5	hyper				150	424	2.18	
	8.1					2529	290	2.97	
	6.1					350	168	8.63	
	6.9					188	1633		
	hypocalcemia		73□23	2.76□0.69	8.53□0.77	1501	596		
4.43□1.77	ND	ND				3051	1335		
	6.98□0.95	M:7.67				1175	2170		
		SD:0.92				6400	855		
						1734	420		

												566	1561
												10500	3200
												5800	1657
												139	104
												1350	1055
												84	104
												4420	4557
												420	
												8755	
												NND	NND
												Q1=150	Q1=141.5
												Q2=1262.5	Q2=725.5
												Q3=3051	Q3=1597
												IQR=2901	IQR=1455.5
												Median=1262.5	
												Min=78	Min=52
												Max=10500	Max=4557
												Ran=10422	Ran=4505

Table S6a. Treatment modalities in patients with henna-induced pigment nephropathy.

Oxygen inhalation	Prednisolon	HCO3	Hydration	Dexamethasone	urine alkaline	forced diuresis	Gastric decontamination	AF fistula	Atenolol	HD	PRBC	Hospital course	Treatment
				+						intermittent			Gowda
	40 mg												Brown 1
	20 mg												Brown 2

			+									+	+		Khine
								+				+			Singla
												+	+		Qurashi
						+				+	100 mg	+			Minoo
		+	+	+											Asgari
+												+			Kaballo
		+	40 ml/kg N/S					+							Chaudran
			+			+	+								Beshir
+		+	+			+	+								Handyal
		+				+	+					+			samputkumar1
		+				+	+								samputkumar2
+				+								+	1 unit		Khatua1
												+			Khatua2
			+											improved	Khatua
+						+									Jain
			+			+	+								Nanrang
						+		+							Amira
			+									+			Mendonca
		+, 60 mg	+												Akl
			IV fluid												Katar
+			+			+	+	+							Oner
+		+	IV fluid	+								+			Anuradha
+		150cc/8 hr	IV fluid	16mg/12 hr		+						+			shalaby
													+		soker

+												+		kheir sik
			+			+	+				+			Prabhakaran

AF fistula, arteriovenous fistula; HCO3, bicarbonate; HD, hemodialysis; hr, hour; IV fluid, intravenous fluid; N/S, normal saline; PRBC, packed red blood cell. Positive sign indicates presence of treatment modality.

Table S6b. Continued.

Dobutamin	**Ventilator**	**ICU**	**fasciotomy**	**Internal Foley catheter**	**Antihistamine**	**IV hydrocortisone**	**tracheostomy**	**H2-blockers**	**Antiemetic**	**PD**	**Antibiotic**	**pantoprazole**	**Methyl prednisolon**
			+								+		
										+ emergency			
								+	+		+		
		+											
	+										+		
			not performed		+	+	+			+			
+	+			+									
		+				+	+						
	+	+					+						

					+							
					+							
					+							
				+	+						+	
		+					emergency					
	+			+						+		
									no respons e			500*5 days
	+	+					emergency tracheotomy					IV
				+			emergency tracheotomy					
	+				200 mg, 100 Q6							
	+											

H2-blockers, histamine blockers; ICU, intensive care unit; IV, intravenous; Q, every; PD, peritoneal dialysis. Positive sign indicates treatment modality.

Table S6c. Continued.

Lisinopril	Cefepime	Vancomycin	Diphenhydramine	Famotidine	Ranitidine	Loratadine	Solumedrol	Ryle's tube feed	TPN	CVVHD	Oral Hco3	Oral calcium	Steroids	PE	Ipratropium bromide	Salbutamol	Etophylline	theophylline	PCAB	CVC	Adrenalin	CPR	ET intubation	Pediatric ICU	furosemide	Chlorophenirami ne	dopamine
discontinued	+	+	+	+	+	+	+																+				
																							+				
																							+	+			+
																						high quality			IV	+	
																			+	+	+						
																							+		+		
																							+		+		
															nebulization	neb ulization	IV	IV							IV		

								nebulization	nebulization	IV	IV			IV
														IV
													+	
						IV	+					SC		+
				+	+									
	+	+	+			+							+	
													+	
													+	+
50mg/8hr IV						IV								
+							+						+	
					+									

CPR, cardiopulmonary resuscitation; CVC, central venous catheter; CVVHD, continuous venovenous hemodialysis; ET, endotracheal intubation; HCO3, bicarbonate; ICU, intensive care unit; IV, intravenous; PE, plasma exchange; PCAB, post-cardiac arrest bundle; Sc, subcutaneous; TPN, total parenteral nutrition

Table S6d. Continued.

Phos binders	Ceftriaxone	CAVH	ECMO	CVVHDF	Anti-edema	Calcium gluconate	Vitamin k	folic acid	fluxacillin	Chloropheniramine	Adrenalin	phenytoin	phenobarbital	FFP	Vasopressors	Valtrex	CRRT
															hold	+	+
		+															
	+																
												+	+	2 unit			

	not use	+	+	+	+	+	1gr/8 hr	4-6 mg IV	Sc 0.25+2.5 N/S	+	+
+											

CAVH, continuous arteriovenous hemodialysis; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenohemodiafiltration; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; IV, intravenous; Sc, subcutaneous. Positive sign indicates presence of treatment modalities.

Table S7. Imaging techniques in patients with henna-induced pigment nephropathy.

Ultrasound scan	**Abdominal CT scan**	**Brain CT scan**	**CT scan-neck**	**EMG**	**NCV**	**Gastroscopy**	**Skull x-ray**	**Abdominal sonography**	**Echocardiography**	**DMSA scan**	**Renal US**	**ECG**	**CXR**	**Imaging**
			soft tissue									Abnormal		Gowda
														Brown 1
												non-reversible VF		Brown 2
											nl			Khine
														Singla
														Qurashi
							nl		EF:45%	cortical defect	Rt small, multiple			Minoo

				nl		nl	increased air lev	Asgari
			acute gas erosion	nl		prominent pyramid, CMD loss	nl	Kaballo
								Chaudran
bilateral bulky kidney								
							nl	Beshir
					EF=20-25%			
								Handyal samputh kumar1 samputh kumar2
								Katua
								Katua
								Katua
						nl		Jain Nandrang
		nl					nl	Amira
							pneumonia	Mendonca
						Hyperechogenic		Akl
	subarachnoid hemorrhage						nl	Katar
								Oner
							ST, Tall T-wave nl	Anuradha
								shalaby

							nl		nl			soker kheir
	free fluid collection	diffuse edema, ICH										sik
							Prolonged PR Prolonged QRS multiple V&SV ectopies+ST changes					
									increased cortical echogenicity			

CT, computed tomography; CXR, chest x-ray; DMSA, dimercaptosuccinic acid; ECG, electrocardiography; EF, ejection fraction; EMG, electromyography; ICH, intracerebral hemorrhage; NCV, nerve conduction velocity; SV, supraventricular; US, ultrasonography; VF, ventricular fibrillation; nl, normal; V, ventricular.

Table S8a. Follow up of patients with henna-induced pigment nephropathy.

Postmortem biopsy	**Died**	**HD**	**Indirect bilirubin**	**Hb**	**Reticulocyte**	**Direct bilirubin**	**Total bilirubin**	**ALT**	**AST**	**SCr**	**Bun**	**clinical recovery**	**Follow up**
	+											deterioration	Gowda
-, small kidneys	+												Brown 1
MI, WG, enlarged	+												Brown 2
				15.5 g/dl						105 micro		+	Khine
	+			13 g/dl						8.9 mg/dl			Singla
		+, d/c		9.5 g/dl		51 mmol/l	73 mmol/l		42 U/l	663 micro/l	29.3 mmol/l	+	Qurashi

		HD							Minoo
				nl	nl	nl	nl	improved	Asgari
		for 3 wk				nl	nl		Kaballo
						1.2		improved	Chaudran
			15 micro/l	149 U/l	170 U/l	80 micro/l			Beshir
		-		121 U/l	745 U/l			gradually	Handyal
	+							saved	samputhkumar1
								%+	samputhkumar2
						nl	nl	asymptomatic	Khatua1
	+							deteriorate	Khatua2
								asymptomatic	Khatua3
						nl	nl	stabilized	Jain
								improve	Nanrang
						677µmol/l	46.4 mmol/l		Amira
	+			decreased	decreased			gradually worse	Mendonca
						0.69 mg/dl	8.98 mg/dl	good	Akl
								neurologic sequella	Katar
				41 U/l	15 U/l	1.1 mg/dl		+	Oner
	+	+							Anuradha
		+						+	Shalaby
								+	soker
								+	kheir

		+			0.99 mg/dl		2.9 mg/dl	1963 U/l	4216 U/l	0.69 mg/dl		hypotension	Sik	
												+	Prabhakaran	

ALT, alanine transaminase; AST, aspartate aminotransferase; Bun, blood urea nitrogen; Hb, hemoglobin; HD, hemodialysis; MI, myocardial infarction; nl, normal; SCr, serum creatinine; WG, Wegener granulomatosis. Positive sign indicates presence and negative sign shows absence of symptom or function.

Table S8b. Continued.

liquid diet	**walking with support**	**Lower extremity**	**Albumin**	**total protein**	**K**	**Na**	**Calcium**	**Biochemical recover**	**Hemolysis**	**urine output**	**Discharge**	**Antibiotic therapy**	**VAP**	**fever**
					nl	nl				2 l/day	+			
			36 g/l	61	3.9	133	2.1 mmol/l	+			+			
											one month	+	+	+
		Improvement of LL after dialysis									+			
+	+										+			
			38	80	3.9	135				+	+			
										> 200 ml/hr				

		increased	+
			+
			+
		1200/day	+
		satisfactory	
			+
	4. 4		+
			+
			+
		+	
	+	+	+

LL, lower limb; VAP, ventilator associated pneumonia. Positive sign indicates presence and negative sign shows absence of item.

Table S8c. Continued.

Patient training	Time-recovery	Respiratory Function	SA	plasma cadmium	plasma lead	Urea	Tracheostomy	Depression	Globulin	Alkaline phosphatase	CPK	Echocardiography
	7 wk					nl 150 mg/dl						
	6 wk											
	4 wk											
	3 wk											
	16 days										30080 U/l	EF:57%
	15 days					13.9 mmol/l		+	42	76	704 U/l	
	6 days										14121 U/l	
	7 days											
	15 days											
	15 days											
	5 days											
	20 days						closed					
	2 wk			< 1	30-169	46.4 mmol/l						
											decreased	

	2 wk												
	40 days	improved		decreased									
	11 days						site close, decannulated				165		
	10 days												
	11 days												
+	6 wk				30 mg/dl								
	One month												

CPK, creatine phosphokinase; Wk, week; nl, normal; SA, spontaneous activity.

Table S8d. Continued.

Differential	G6PD level	Plt	WBC	Cause	Psychiatrist	Family education	CVVHDF	PE	Vasopressor	Lactate	PTT	PT	INR
				cardiac arrest									
				coliform Bronchopneumonia irreversible Ventricular fibrillation									
	78.98 mU/10	320000	6400										
P72/L28			10000										
P69/L15.8			16.6										

				+					
	hemodynamic instability								
	HAP/sepsis								
	cardiac arrest								
				+					
3.1 U/g									
	refractory VF	+	+	+		1.7 mmol/l	46.2	24.6	1.98

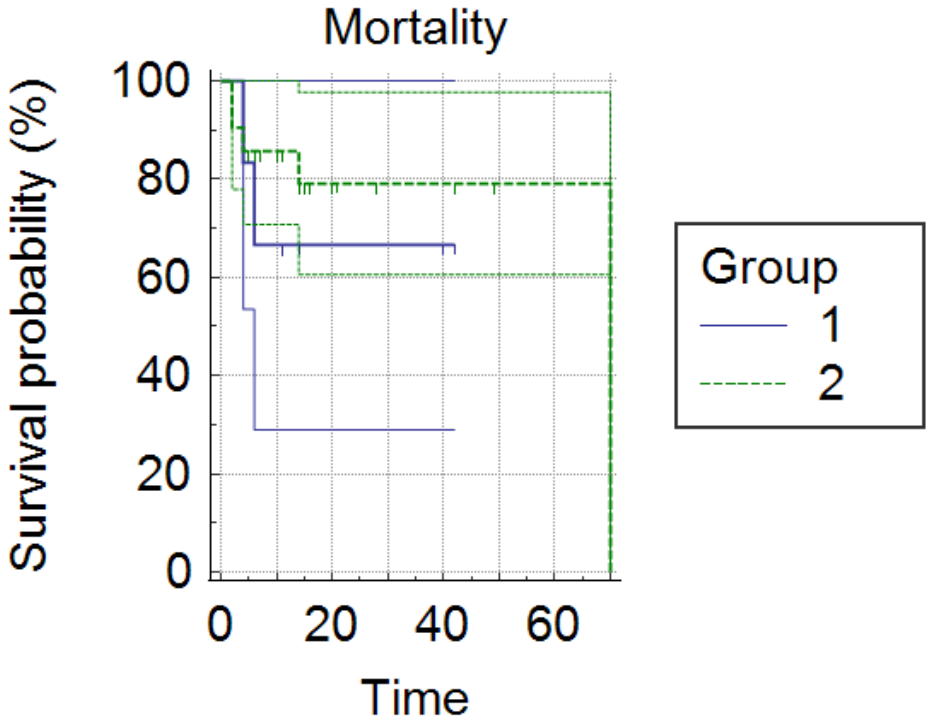
CVVHDF, continuous venovenous hemodiafiltration; G6PD, glucose-6-phospahate dehydrogenase; INR, internationalized normal ratio; HAP, hospital associated pneumonia; Plt, platelet; PT, prothrombin time; PTT, partial thromboplastin time; PE, plasma exchange; WBC, white blood cell count. Positive sign indicates presence and negative sign shows absence of item.

Table S8e. Continued.

SCr1(before HD)	SCr2(post HD)	SCr1(baseline)	SCr2(follow/up)	Time-death	Urea	CPK	Na	serca	Hb	D.bili	T.bili	ALT	AST	Bun	SCr	time		Uric acid	CAVH	Trans toward	AV fistula
11.46	2.76	0.7	8.9	6 days	150	30080	133	8.4 mg/dl	9.5	2.95	4.23	149	42	82.04	8.9	13 days	AKD				
0.7	9	1.56	7.49	?	83.4	704				0.99	0.87	121	170	129.94	7.49	5 days	AKI				
1.55	7.49	3.35	7.65	?	278.4	14121					2.9	41	745		7.65	1.5 days	AKI				
12	nl (less than 1.3)	0.9	1.1			165						1963	4216		0.69 (CVVHDF)	3 days	AKI				
9.5	2.5	1.13	0.69(CVVHDF)	14 days										109.67 ±20.27							
		1.6	1.2		170.36 ±80.93	11267.5 ±12215.82				1.97 ±0.98	2.66 ±1.38	median:135 NND range:1922	1293.25 ±1708.09								pos
																				pos	

	2 days							
			Mortality	correlation				positive
			SCr					
	4 days							
	10 wk							
							3.9 mg/dl	
	2 days							
	4 days							
								observation

AKI, acute kidney injury; AKD, acute Kidney disease; AV, arteriovenous fistula; ND, normal distributed; NND, non-normal distributed; SCr, serum creatinine; Wk, week.



Kaplan-Meier survival analysis

Data

Group	Time	Mortality

1	6	1
2	49	0
2	14	1
2	42	0
2	28	0
2	21	0
2	16	0
2	15	0
2	6	0
2	2	1
2	7	0
2	15	0
2	4	1
2	15	0
2	5	0
2	20	0
2	14	0
2	70	1
1	14	0
1	40	0
2	11	0
2	2	1
2	10	0
1	11	0
1	42	0
1	4	1
2	28	0

Kaplan-Meier survival analysis

Survival time	Time
Endpoint	Mortality
Factor codes	Group

Cases summary

	Number of events [a]		Number censored [b]		
Factor	N	%	N	%	Total sample size
1	2	33.33	4	66.67	6
2	5	23.81	16	76.19	21
Overall	7	25.93	20	74.07	27

[a] Mortality = 1
[b] Mortality = 0

Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
1	29.667	7.125	15.703 to 43.631	-	
2	56.689	6.685	43.586 to 69.791	70.000	70.000 to 70.000
Overall	54.750	5.925	43.138 to 66.362	70.000	70.000 to 70.000

Survival table [Hide]

	Factor				Overall	
	1		2			
Survival time	Survival Proportion	Standard Error	Survival Proportion	Standard Error	Survival Proportion	Standard Error
2	-	-	0.905	0.0641	0.926	0.0504
4	0.833	0.152	0.857	0.0764	0.852	0.0684
5	-	-	-	-	-	-
6	0.667	0.192	-	-	0.813	0.0754
7	-	-	-	-	-	-
10	-	-	-	-	-	-
11	-	-	-	-	-	-
14	-	-	0.791	0.0948	0.762	0.0862
15	-	-	-	-	-	-
16	-	-	-	-	-	-
20	-	-	-	-	-	-
21	-	-	-	-	-	-
28	-	-	-	-	-	-
40	-	-	-	-	-	-
42	-	-	-	-	-	-
49	-	-	-	-	-	-
70	-	-	0.000	0.000	0.000	0.000
Endpoint: Observed n		2.0		5.0		
Expected n		1.3		5.7		
Observed/Expected		1.4934		0.8833		

Comparison of survival curves (Logrank test)

Chi-squared	0.4323
DF	1
Significance	P = 0.5108

Hazard ratios[a] with 95% Confidence Interval

Factor	1	2
1	-	0.5198 0.07393 to 3.6548
2	1.9237 0.2736 to 13.5258	-

[a] Column/Row

Group 1: Topical/inhalational henna

Group 2: Oral mixed henna

Code 0: survival

Code 1: Death