Available online on www.ijtpr.com
International Journal of Toxicological and Pharmacological Research 2013; 5(1): 26-29

ISSN: 0975-5160

Research Article

N Acetyl Cysteine treatment plus standard care reduces duration of mechanical ventilation in hair dye poisoning

[1]Kondle Raghu, *[2]Pathapati Rama Mohan, [1]Saginella Satish Kumar, [1]Malliboina Srinivas, [2]Sujith Tumkur Rajashekar, [3]B. V. Subramanyam, [2]Madhavulu Buchineni

[1]Emergency Medicine, Narayana Medical College Chintharedypalem, Nellore, Andhra Pradesh, South India
[2]Pharmacology, Narayana Medical College Chintharedypalem, Nellore, Andhra Pradesh, South India
[3]Forensic medicine and Toxicology Narayana Medical College Chintharedypalem, Nellore, Andhra Pradesh, South India

ABSTRACT

Poisoning is one of the preferred means of suicide and Para-phenylenediamine (PPD), a common chromophoric ingredient in oxidative hair-dyes, is frequently used for this purpose. Crude estimates reveal that more than 500 patients received treatment for hair dye poisoning in our region. Reports have shown that increased free radical formation in PPD poisoning. N-acetylcysteine (NAC) is an antioxidant, both directly as a glutathione substitute and indirectly as a precursor for glutathione. In order to evaluate if the inclusion of NAC in the treatment of poisoning with PDD could be beneficial, a single center open label quasi experimental study was conducted at our hospital. We found that there was a significant reduction in the duration of ventilator support in the patients who received NAC (3.13±1.5days) as compared to patients who received standard care only (6.25±3.85 days) (p=0.01). However the duration of hospital stay was not statistically different. (p=0.56). Our results suggest that the inclusion of NAC treatment into standard care in hair dye poisoning may reduce duration of ICU stay and could thus be superior to standard care only.

Keywords- Para-phenylenediamine, N-Acetylcysteine, N-acetetyltransferase, Glutathione, Acute kidney injury

INTRODUCTION

Hair dye poisoning occurs when someone swallow dye. An increasing trend has been observed in accidental and intentional cause of poisoning has been reported from various parts of Andhra Pradesh. Crude estimates reveal that more than 500 patients received treatment for hair dye poisoning in our region. [1, 2] Hair dye contains paraphenylene-diamine and a mixture of other chemicals that can damage the respiratory, muscular, renal and hepatic systems and cause death. Reports have shown that increased oxidative stress depletes glutathione in the tissues and makes the latter more sensitive to tissue injury. [3] Re-establishment of a supply of antioxidants in standard therapy may improve the clinical outcomes. N-Acetylcysteine (NAC), an antioxidant is used in patients with paracetomol poisoning. It is also used in patients receiving contrast dye for x-rays and has been shown to reduce detrimental effects on kidney function compared to patients not receiving NAC. NAC is also used in non acetaminophen induced acute liver failure. [4] In the present study, we assessed the efficacy and safety of N Acetyl Cysteine treatment plus standard care in hair dye poisoning and compared with the historical controls who received with standard care only.

METHODS

This is a single center open label quasi experimental study conducted at our hospital. Institutional ethics committee approved the study protocol (262-IEC/NMCH-dated 10/03/2012). Informed consent was obtained at admission from legally acceptable representative and at recovery from patient. 15 consecutive patients received NAC along with standard care. Patients were included if they had consumed hair dye and if they were willing to give consent. Patients were excluded if they had previous history of NAC Allergy and Acetaminophen intoxication.

Standard treatment includes gastric lavage, antihistamines, parenteral steroids and alkalinization of the urine. Respiratory distress is the major early challenge, which may require ventilator support. Renal support in the form of dialysis is required in acute renal failure. N-Acetyl Cysteine was given as infusion at 150mg/kg bolus dose at admission then next 4-6 h 50 mg/kg infusion and from 6-24 hrs100mg/kg infusion. From day two till discharge 400 mg twice daily as bolus doses. Biochemical and other blood parameters determined at admission and every alternative day till discharge from hospital. Endpoint points were safety, duration of ventilator support, length of hospital stay and time to normalization of lab parameters. Additionally, comparison was made with historical controls (HC) defined as the patients who received standard treatment only.

STATISTICAL ANALYSIS

The data was collected in the case record forms and were transferred to Microsoft excel spreadsheet 2007

Author for correspondence: E-mail:Pill4ill@yahoo.co.in

Table-Comparison of parameters between Historical Controls and N- Acetyl Cysteine Groups

Parameters	Historical Controls	Standard Treatment + N acetyl- Cysteine	P Value
Age (yrs)	20.88±4.22	25.73±10.45	0.22
Gender (M/F)	0/8	4/11	0.30
Time to admission (hours)	5.88±3.00	8.64±4.97	0.16
Hemoglobin (g/dL)	10.59±1.98	11.03±1.99	0.61
Volume of Consumption (mL)	100±10.12	101.66±14.84	0.78
Cervicofacial edema	8	14	0.74
Oliguria	0	2	0.76
Seizures	0	1	0.74
Total white blood cell count (cells/mm3)	20152.50±6429.91	16333.33±5576.82	0.15
Serum Calcium (mg/dL)	7.94±0.77	8.14±1.1	0.65
Serum creatinine (mg/dl)	1.35±1.12	0.94±0.21	0.17
Serum creatinine phosphokinase (U/L)	32993.50±16923.45	34586.07±32898.52	0.89
Serum SGOT (U/L)	2359.13±1515.01	1272.33±909.60	0.04
Serum SGPT (U/L)	1656.38±1907.80	325±372.70	0.01
Serum alkaline phosphatase (U/L)	290.00±167.97	162.33±56.36	0.01
Patients requiring dialysis	1	1	0.76
Mortality	1	0	0.11
Duration of Ventilator Support (days)	6.25±3.85	3.13±1.54	0.01
Duration of Hospital Stay (days)	9.13±4.09	10.07±3.40	0.56

(Microsoft Corp, Seattle, WA, USA). The statistical analysis was executed by Graph pad prism software, USA Version-4. Continuous data was presented as mean, median, range and standard deviation. Between groups, analyses were carried out by using "t-" test. Categorical data was presented as actual numbers and percentages. Categorical variables were analyzed with "Fischer's exact test." For statistical significance, the probability value of less than 0.05 was considered.

RESULTS

Fifteen patients were studied out of them there were 4 males and 11 females in NAC group. There were only 8 females in HC group. The mean age of the patients in the HC group was 20.88±4.22 where as it was 25.73±10.45 (p=0.22) years in patients who received NAC along with standard treatment. The mean time to hospitalization was similar across the HC vs. NAC groups were 5.88±3.00 vs. 8.64±4.97 (p=0.16) hrs respectively. The classical features of hair dye poisoning such as cervicofacial edema with the hard protruding tongue was observed in 8 (100%) &14(90%), Oliguria 0% & 2(13%), seizures 0% and 1 (6%) patient in controls and in NAC group respectively. It can be noticed from the table-1 that the biochemical parameters were also similar across the two groups except for liver parameters which were statistically higher in HC group than NAC group. There was a significant reduction in the duration of ventilator support in the patients who received NAC 3.13±1.5days than patients who received standard care only 6.25±3.85 days (p=0.01). However the duration of hospital stay was not statistically different 9.13±4.09 *vs.* 10.07±3.40days (p=0.56). In NAC group, one patient developed ARF after 36 hours of poisoning and recovered with hemodialysis. Three patients showed inversion of T waves in ECG, one patient underwent tracheostomy and no deaths were observed. None of the patients developed adverse drug reactions.

DISCUSSION

Hair dye poisoning has become another major source of poisoning next to pesticides because of its easy availability and low cost. The features of poisoning were observed with consumption of even lower volumes such as 25mL. With large volumes, there was an increase in morbidity such as patients needing ventilator support, duration of hospital stay and mortality. The classical features of acute poisoning was seen within six hrs, untreated patients developed full blown picture of poisoning between 6-12 hrs. Clinical features include cervicofacial edema accompanied by a swollen, dry, hard and protruding tongue, acidosis, hepatitis, rhabdomyolysis-induced myoglobinuric acute renal failure (ARF). [(5)]

Reports have shown that increased free radical formation in PPD poisoning [(6)] which may be responsible for the deleterious effects on tissues. The glutathione levels (GSH) were depleted with increase of time suggesting decrease of anti-oxidant status in PPD poisoning. Antioxidant GSH plays a vital role in scavenging of reactive oxygen species, maintenance of cell viability, DNA replication, regulation of immune cell functions and

apoptosis. [3] N-acetylcysteine (NAC) acts as an antioxidant, both directly as a glutathione substitute and indirectly as a precursor for glutathione. NAC causes inhibition of COX 1 mediated action of xenobiotics, expression of COX 2[7-12] hence prostaglandin formation was completely inhibited in cells pre-stimulated with the anti-oxidant *N*-acetylcysteine. [13] NAC also inhibits TNF-α production. [14]

Supplementation with antioxidants in standard therapy may improve the clinical outcomes. To the best of our knowledge this is the first report using NAC as an add-on therapy to standard care for hair dye poisoning. Our study reports suggest that addition of NAC to standard care significantly reduces the duration of ventilation support as compared to historical controls.

Paraphenylene-diamine is catalyzed by the phase II enzymes N-acetetyltransferase type 1 and type 2 (NAT1 and 2) [15-17] CYP1A family is also involved in the activation and detoxification of PPD and other exogenous (aryl-) amines. [18] Abnormal high exposure (intoxication) to PPD leads to saturation of the NAT1 and NAT2 enzymes resulting in the urinary excretion of the un-metabolized compound. Molecular epidemiological studies have suggested that polymorphisms in genes encoding metabolizing enzymes may influence the individual's susceptibility for sensitization to PPD. [19]

In our study we found that there was significant reduction in duration of ventilatory support in NAC treated group as compared to Historical controls. The probable mechanism may be due to antioxidant and anti-inflammatory activity of NAC. Our study findings are similar to a prospective randomized, controlled trial conducted by Suter et al, [20] who reported that enhanced recovery for patients with acute lung injury when treated with NAC, with a shorter but not statistically significant ventilation time, and increased oxygenation index.

However, there was no significant difference in duration of hospital stay and mortality in both NAC treated as well as Historical controls. This finding is similar to another study of Suter et al [21] where NAC was compared to placebo in acute respiratory distress syndrome (ARDS). Bernard et al [22] also found no difference in mortality, but found lower acute lung injury scores in both of the treatment groups compared with the control group in a prospective double blind randomized controlled trial of NAC versus placebo in patients with ARDS.

The probable reasons for decrease in duration of ventilator support could be due to decrease in the liver toxicity markers suggests lower toxicity in the liver and patient overall, which could explain the lower ventilation time for the NAC-treated patients during critical phase of recovery. However, the reasons for non- significance in duration of hospital stay may be social, economical, literacy, experience of physician, logistics and sentiments of patient's family.

Study limitations-Our study was a quasi experimental study, hence the results should be interpreted with caution because of small sample size. We could not compare time to normalization of biochemical parameters as the data for historical controls was not available. However further studies are required involving larger sample size to find the true benefits of NAC in hair dye poisoning.

CONCLUSION

NAC as an add-on to the standard care in hair dye poisoning reduces the duration of ventilator support in hospital. It is cost effective as well. Liver morbidity also appears to be decreased by NAC as indicated by laboratory parameters.

Conflict Of Intrest: None

REFERENCES

1. D Radhika KV Murali Mohan M Sreenivasulu YR Srikanth TS Karthik (2012). Hair Dye Poisoning-A Clinicopathological Approach and Review. J Biosci Tech, 3; 5: 492- 497.
2. Raghu Kondle, Rama Mohan Pathapati, Satish Kumar Saginela, Srinivas Malliboina, Veera Prasad Makineedi (2012). Clinical profile and outcomes of Hair Dye Poisoning in a Teaching Hospital at Nellore. ISRN Emergency Medicine Article ID 624253, 5 pages
3. Srinivas Sutrapu, Jagadeeshwar K, Nagulu M, Vidyasagar (2010). J Oxidative Stress and Anti-oxidant Status in Hair Dye Poisoning. International Journal of Pharmacognosy and Phytochemical Research 3;1:1-5.
4. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, Davern TJ 2nd, Murray NG, McCashland T, Reisch JS, Robuck PR (2009). Acute Liver Failure Study Group Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 137; 3:856-64.
5. Mohamed Abdelraheema, Mohamed Hamdoukb, Eduard E Zijlstrac (2010). Paraphenylene Diamine (Hair Dye) Poisoning in Children. Arab Journal of Nephrology and Transplantation : 3;1: 39-43.
6. Krishnaswamy, Sampathkumar, Sooraj Yesudas (2009). Hair dye poisoning and the developing world. J Emerg Trauma Shock. 2; 2: 129-131.
7. MC Atkinson (2002). The Use of N-Acetylcysteine in Intensive Care. Critical Care and Resuscitation 4; 1: 21-27.
8. Rioux N, Castonguay A (2000). The induction of cyclooxygenase-1 by a tobacco carcinogen in U937 human macrophages is correlated to the activation of NF-kappaB. Carcinogenesis : 21;9:1745-51. Chinery R, Beauchamp RD, Shyr Y, Kirkland SC, Coffey RJ, Morrow JD (1998).
9. Antioxidants reduce cyclooxygenase-2 expression, prostaglandin production, and proliferation in colorectal cancer cells. Cancer Res., 58;11:2323-7.
10. Yan Z, Subbaramaiah K, Camilli T, Zhang F, Tanabe T, McCaffrey TA, Dannenberg AJ, Weksler BB (2000). Benzopyrene induces the transcription of cyclooxygenase-2 in vascular smooth muscle cells. Evidence for the involvement of extracellular signal-regulated kinase and NF-kappaB. J Biol Chem 275; 7:4949-55.

11. Davreux CJ, Soric I, Nathens AB, Watson RW, McGilvray ID, Suntres ZE, Shek PN, Rotstein OD (1997). N-acetyl cysteine attenuates acute lung injury in the rat. Shock 8; 6:432-8.
12. El-Kadi AO, Bleau AM, Dumont I, Maurice H, du Souich P (2000). Role of reactive oxygen intermediates in the decrease of hepatic cytochrome P450 activity by serum of humans and rabbits with an acute inflammatory reaction. Drug Metab Dispos., 28; 9:1112-20.
13. Ruth Moeller, Jutta Lichter, Brunhilde Blömeke (2008). Impact of para-phenylenediamine on cyclooxygenases expression and prostaglandin formation in human immortalized keratinocytes (HaCaT). Toxicology 249; 2–3: 167–175.
14. Oka S, Kamata H, Kamata K, Yagisawa H, Hirata H (2000). N-acetylcysteine suppresses TNF-induced NF-kappaB activation through inhibition of IkappaB kinases FEBS Lett. 472;2-3:196-202.
15. Hu T, Bailey RE, Morra ll SW, Aardema M J, Stanley LA, et al. (2009). Dermal penetration and metabolism of p-amino phenol and p-phenylene diamine : application of the EpiDermhuman reconstructed epidermis model. Toxicol Lett 188: 119–129.
16. Barker DF, Walraven JM, R istagno EH, Doll MA, States JC, et al. (2008). Quantitative tissue and gene-specific differences and developmental changes in Nat1, Na t2, and N at3 mRNA expression in the rat. Drug Metab Dispos 36: 2445–2451.
17. Sim E , Lack N, Wang CJ, Long H , Westwood I, et al. (2008). Arylamine N -acetyltransf erases: structural and function al implications of polymorphisms. Toxicology 254: 170–183.
18. Nebert DW, Dalton TP, Okey AB, Gonzalez FJ (2004). Role of aryl hydrocarbon receptor-mediated induction of the CYP 1 enzymes in environmental toxicity and cancer. J B iol Chem., 279; 238:47–50.
19. 19.Brans R, Skazik C, Merk HF, Blömeke B (2009). Sensitisation to p-Phenylenediamine. Effects of metabolism and individual susceptibility. Hautarzt. 60; 1:26-31.
20. Suter PM, Domenighetti G, Schaller MD, Laverriere, Ritz R, Perret C (1994). N-acetylcysteine enhances recovery from acute lung injury in man, a randomised double-blind, placebo-controlled clinincal study. Chest., 105:190-194.
21. Domenighetti G, Suter PM, Schaller MD, Ritz R, Perret C (1997). Treatment with N-acetylcysteine during acute respiratory distress: a randomized double-blind placebo-controlled clinical study. J Crit Care., 12:177-182.
22. Bernard GR, Wheeler AP, Arons MM, et al. (1997). A trial of antioxidants N-acetylcysteine and procysteine in acute respiratory distress syndrome. Chest., 112:164-1