

Prevalence of Acute Renal Failure Due to Exogenous Nephrotoxins in Ilorin

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ABSTRACT

A study was carried out to see how many cases of acute renal failure (ARF) due to exogenous nephrotoxins were recorded at the nephrology unit of University of Ilorin Teaching Hospital over a five year (Jan 1998-Dec. 2002) period. The patients were analyzed with specific reference to age, sex, type of toxins, duration of illness, treatment modalities and prognosis. Thirteen cases (7 males, 6 females) of nephrotoxic ARF were identified out of 118 (11%) ARF cases seen within the period. It ranked 4 to Septicaemia (32%), severe Gastroenteritis (21%) and acute Glomerulonephritis(12%) as a cause of ARF in the study. Age range was 19-45 years with a mean of 35 years. Non steroidal anti-inflammatory drugs (NSAID) were the commonest (38%) implicated toxic agent, followed by co-administration of herbal preparations (31%), while heavy alcohol intake, herbal vaginal pessary insertion and consumption of "holy green water" accounted for 5% respectively. Five cases (39%) were complicated by septicaemia of which 3 that benefited from haemodialysis recovered. All patients (100%) that had haemodialysis survived in contrast with 78% of cases managed conservatively. Majority of the patients (85%) were oliguric at presentation and overall mortality rate was 15%. It is concluded that ARF due to exogenous nephrotoxins is not uncommon in our environment, the toxins are potentially preventable and prognosis is better with dialysis therapy.

Keywords: *ARF, nephrotoxins, anagement, prognosis*

INTRODUCTION

Acute Renal failure (ARF) is a syndrome characterized by rapid deterioration in renal function, resulting in accumulation of nitrogenous waste products sufficient to cause ureamia following a variety of insults to previously normal kidneys[1-3]. It is a frequently encountered clinical condition worldwide and a common cause of morbidity and mortality in Nigeria[1-6]. Although the causes are many and often multifactorial, those resulting in acute prerenal azotaemia and acute tubular necrosis are the most common. Majority of the causative factors are largely preventable and potentially reversible if recognized early and promptly treated [2, 5-8]. The management and prognosis of severe ARF is capital intensive and carries a gloomy picture even though majority of identifiable causes are potentially preventable. In view of the scarcity of renal substitution therapy and poor financial status of patients in Nigeria, adequate knowledge on the prevalence and pattern of ARF will assist in formulating rational preventive nephrology policy. Acute renal failure due to exogenous nephrotoxins like drugs and herbal remedies which cause toxic and/or ischaemic structural injury to the kidney are infrequently reported in our environment [7, 9, 10]. Unfortunately, the human kidney is particularly vulnerable to toxin induced injury for reasons of being highly vascularized per gram of tissue, possessing the largest endothelial surface by weight of any other organ in the body and it's ability to ultrafiltrate and concentrate blood-borne nephrotoxins[11, 12].

The clinical importance of our knowledge about nephrotoxicity due to drugs and herbal remedies are that these agents not only cause acute toxic effects but can act insidiously culminating in chronic kidney disease and death after a long latent period [9,10, 13]. A lot of these agents are consumed in urban and

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rural areas for human ailments without defined duration. The exact prevalence and outcome of ARF due to toxic nephropathy is not known in Ilorin, but there is strong suspicion that it may be high judging from the way people consume analgesics and herbal preparations for illnesses before seeking medical attention. This retrospective study is an attempt to define the magnitude and outcome of ARF due to drugs and herbal remedies seen in a tertiary hospital.

PATIENTS AND METHODS

All adult patients with confirmed ARF that presented to the nephrology unit of the University of Ilorin Teaching Hospital (UIH) within five year period (January 1998-December 2002) were studied with specific reference to those due to exogenous nephrotoxins. The study excluded ARF in surgical and obstetric practices. The inclusion criteria for the diagnosis of ARF in this study comprised of some or all of the following features: Short duration of illness, unusual weakness, vomiting, anorexia, hiccups, diarrhea, oliguria, anuria, polyuria, loin pain, pruritus, bleeding tendency, body swelling and altered sensorium. Biochemical evidence of moderate to severe renal insufficiency like raised blood level of urea, creatinine, uric acid and phosphate and low calcium and bicarbonate. The presence of diminished glomerular filtration rate in a setting of normal sized kidneys. The exclusion criteria were previous history of renal disease, more than six months duration of illness, ultrasonic evidence of shrunken kidneys and presence of clinical features of ARF without laboratory results due to financial constraints. A urine output of less than 400mls/day typifies oliguric ARF while output of more than 400mls/day denotes non-oliguric ARF. All the patients had ultrasonographic evaluation and relevant blood and urine tests after detailed history and physical examination aimed at excluding other causes of ARF. Majority of the aetiological factors were obtained from the clinical features. All patients in whom septicemia were suspected had septic work-up and virtually all showed leukocytosis and toxic granulations with vacuolation of neutrophils on peripheral blood film. The diagnosis of acute glomerulonephritis was based on the presence of facial swelling and/or ankle oedema, macroscopic haematuria, hypertension and mild proteinuria. They did not have renal biopsy. There were 118 cases of ARF and 13 (7males and 6 females) satisfied inclusion criteria for ARF due to

exogenous nephrotoxins and these include the following:

1. Sudden onset of the aforementioned clinical features of renal failure of few days to one week duration
2. History of ingestion of drugs or herbal remedies antedating the ARF for few days to one week.
3. History and/or presence of skin rashes, body itching and fever.
4. Peripheral blood evidence of eosinophilia.
5. Clinical, biochemical or hematological evidence of haemolytic jaundice or hepatocellular damage.
6. Presence of microscopic haematuria, eosinophiluria or white blood cell casts in the urine.

All the patients were commenced on conservative management and those that failed to maintain good quality of life and could afford renal replacement therapy were dialysed. The conservative treatment were dependent on primary cause, precipitating factors, phase of ARF, presence of complications and co-morbid conditions. This included fluid administration and /or restriction, low protein diet of 30-40gms per day, low phosphate, low salt and high carbohydrate diet providing 2500-3500 calories daily, correction of anaemia by use of haematinics and/or blood transfusion, control of edema, hypertension, and infection with appropriate diuretics, antihypertensive and antibiotics, discontinuation of offending agent and counseling by psychiatrist. Renal replacement therapy was by hemodialysis using AK10 Gambro or Fresenius machines, hollow fibre dialysers and blood lines through femoral cannulation

Analyses of the patients were by multiway frequency table and simple proportion with specific reference to age, sex, causative factors, duration of illness, treatment modalities and outcome.

RESULTS

A total of 118 patients with ARF were documented in the study. Table 1 depicts the categories and frequency of the cases. Septicaemia (32%), severe gastroenteritis (21%) acute glomerulonephritis (12%), nephrotoxins (11%) and obstructive uropathy (7%) were the main causes of ARF. Thirteen cases (7 males, 6 females) of nephrotoxic ARF were identified out of 118 (11%) ARF cases seen within the study period (table 2). The age range was 19-45 years

Table 1: Categories and frequency of ARF in Ilorin

Causes	No of Patients	% of Total
Septicaemia	38	32.20
Severe Gastroenteritis	25	21.19
Acute Glomerulonephritis	14	11.86
Drugs, holy water and Herbal remedies	13	11.02
Obstructive uropathy	8	6.78
APH and PPH	5	4.24
Acute Pyelonephritis	5	4.24
Intravascular Haemolysis	3	2.54
Septic Abortion	3	2.54
Unknown	4	3.39
Total	118	100

Table 2: Multiway frequency table

Age	Sex	Causes	Co-morbid	Duration	Treatment	Outcome
35	F	NSAID	-	12 days	Conservative	Discharged
41	M	NSAID	Sepsis	5 weeks	Dialysis	Discharged
45	M	NSAID	Sepsis	7 weeks	Conservative	Died
41	M	NSAID	Sepsis	5 weeks	Dialysis	Discharged
40	F	NSAID	Sepsis	3 weeks	Dialysis	Discharged
30	F	NSAID + Herbs	-	5 weeks	Conservative	Discharged
35	F	NSAID + Herbs	-	1 week	Conservative	Absconded
45	M	NSAID + Herbs	-	8 days	Conservative	Discharged
25	M	NSAID + Herbs	-	5 days	Conservative	Discharged
25	M	NSAID + Herbs	-	3 weeks	Conservative	Absconded
19	F	Herbs	Sepsis	9 days	Conservative	Died
40	F	Herbal Vaginal Pessary	-	3 weeks	Conservative	Discharged
32	M	Holy green water	-	4 days	Dialysis	Discharged

Table 3: Biochemical parameters and occupation of the patients

INITIAL	OCCU	Na	K	Ur	Cr	Ca	PO ₄	Urate
D.J	C/S	132	3.5	30	669	2.02	0.98	0.44
B.T	ST	132	3.2	17.4	496	2.31	0.94	0.55
J.S	TRAD	133	4.5	35.5	423	2.33	1.9	0.65
A.Y	CARPT	129	2.8	33.1	1357	1.64	1.83	0.66
I.F	C/S	136	4.9	25.4	629	2.18	1.98	0.28
A.S	ST	140	5.0	20.1	744	2.18	0.80	0.32
G.S	TECHR	130	6.0	16.5	836	2.20	1.40	0.46
M.S	FAMR	130	7.3	26.4	548	2.43	1.91	0.38
S.A	ST	126	5.0	23.5	653	2.30	1.52	0.45
Y.A	TECHR	143	7.7	17.6	124	1.94	1.25	0.23
Y.K	TRAD	134	4.4	15.9	626	2.49	1.12	0.37
A.A	FAMR	135	5.2	16.5	729	2.50	1.01	0.40
A.T	DRIVR	130	4.0	18.5	915	1.89	1.98	0.60

Note: Cr is in $\mu\text{mol/l}$ and others in mmol/l

OCCU = occupation, C/S= civil servant, ST= Student, Trad=Trader,

Carpt- carpenter, TECHR= Teacher, FAMR= Farmer, DRIVR= Driver.

with a mean of 35 years. Table 3 shows the biochemical parameters and occupation of the patients. Non-steroidal anti-inflammatory drugs (NSAID) were implicated in 5(38%) cases, combination of NSAID and herbal preparation in 5(38%) with one case each (8%) of heavy alcohol intake, herbal vaginal pessary insertion and consumption of "holy green water" (a spiritual preparation of a religious sect). Five cases (38%) were complicated by septicaemia of which 3 that benefited from haemodialysis survived. All the four cases (100%) that had haemodialysis survived while seven out of nine cases (78%) managed conservatively recovered, which suggest the beneficial effect of intervention therapy. Nine cases (69.2%) recovered fully, 2 (15.4%) lost to follow-up and 2 (15.4%) died. Complete recovery was defined as return of the blood urea and serum creatinine value to normal range. It was difficult to compare the outcome between patient that took either herbal remedies or non steroidal anti-inflammatory (NSAID) alone because more than 30% ingested both agents. All the patients that took both NSAID and herbs recovered while one patient who took only herbs died. The poor prognostic factors identified were low socio-economic status and septicaemia.

DISCUSSION

Majority of ARF patients in this study presented in a setting of septicaemic illness in which the primary focus could not be identified and attempts at bacteriological prove was virtually fruitless. The possible contributory factors were abuse of antibiotics prior to presentation, unwillingness to carry out investigations because of poor financial status, inadequate laboratory support, concealment of information and poor recall of events. The diagnosis of sepsis was mainly based on persistent high body temperature, peripheral blood film picture and positive response to antibiotic therapy. Febrile illness was also a prominent feature in many of the patients with severe gastroenteritis, acute glomerulonephritis, toxin induced renal failure and obstructive uropathy. It was noted that none of the diseased patients in whom the cause of ARF could not be found had post mortem examination. This could be attributed to emotional response to grief and unwillingness to accept autopsy due to intense desire to bury relations that are dead intact. It may also be related to believe in life after death or religious injunction that demands burial within 24 hours of death. The kidneys are particularly vulnerable to toxin induced damage for

reasons of being highly vascularized per gram of tissue, possessing the largest exposed endothelial surface by weight of any other organ in the body, presence of active metabolic processes, propensity to develop autoimmune diseases and the ability to ultrafiltrate and concentrate blood borne nephrotoxins[11, 12]. The use of drugs and herbal remedies was responsible for ARF in 11% of the cases studied. This figure is in accord with 10.9% reported by Otieno *et al* [9] in Nairobi but close to 8% and 9% in the studies of Bamgboye *et al* [2] and Ojogwu [10] at Lagos and Benin respectively. It however, contrasts sharply with 33.0% and 35% observed in the studies of Adelekan *et al* [7] and Seedat YK [1] in Ife and Durban respectively. Nephrotoxins have been found from studies to rank second to sepsis as aetiology of ARF in the tropics, [1, 2, 14]. The reasons adduced are occupational exposures to venoms from animals, wide spread use of herbal remedies, exposure to contaminated holy water and consumption of unprescribed drugs bought from street traders. Most of the herbal remedies are neither standardized nor the dose or duration of therapy specified.

Non steroidal anti inflammatory drugs which included piroxicam, Ibuprofen, Aspirin, phensic and "Alabukun" were the commonest (38%) implicated toxic agent in this study followed by co-administration of NSAID and herbal remedies (31%), while heavy alcohol intake, herbal vaginal pessary insertion and consumption of Holy green water were responsible for 8% respectively. Analgesic abuse has been shown to account for 2-30% of end stage renal disease and the wide variation in the prevalence has been attributed to differences in the pattern of analgesic use and diagnostic methods [15-18]. The mechanism of ARF due to NSAID may involve renal hypoperfusion, acute tubular necrosis or acute interstitial nephritis either singly or in combination [19]. These drugs collectively inhibit cyclooxygenase enzyme which catalyzes the formation of prostaglandin from arachidonic acid. The risk of anti-prostaglandin effect of NSAID is increased in hypovolaemic states like liver cirrhosis, heart failure and nephrotic syndrome as the intrarenal levels of angiotensin II are usually high with often compensatory increase in renal synthesis of vasodilatory prostaglandins. These patients often presents with fever, skin rashes, eosinophilia, sterile pyuria, haematuria and non-oliguric ARF. Renal tissue histology finding are usually interstitial oedema, eosinophilic infiltration of the interstitium and tubular changes with normal glomeruli and blood vessels.

Herbal remedies especially as co-administration with NSAID constituted a major source of nephrotoxicity accounting for more than 30% in our patients with toxin induced ARF while it could be clearly blamed in 15% of cases. This figure is close to 11% reported by Dukes *et al* [20] but higher than 4% in Seedat [1] series. One of the major flaws in the foregoing studies is the paucity of histologic diagnosis and documentatio of specific histologic changes due to herbal remedies. In the study by Ojogwu [10], he observed the presence of more severe glomerular lesions apart from the tubulo-interstitial changes in the renal biopsy of those patients who had taken herbal remedies. Although the local remedies are neither measured in the blood and urine nor their composition known, but the recovery and/or improvement in renal function that follow the discontinuation of the offending agents tends to suggest strong cause and effect relationship. "Holy green water" which is often used by a religious sect for healing purposes was responsible for ARF in one of our patients. Similar cases have been reported by Adelekan *et al* [7] in which the prognosis was good. The water is very rich in copper compounds and is thought to be responsible for the haemolytic process in these patients. The mortality rate of 15% observed in this study is still within the range of earlier reports [3, 21- 24]. Mortality rate from ARF depends on the severity, location of patients, length of oliguria, type of treatment modality and presence of co-morbid conditions. A simple ARF in the absence of other underlying illness has about 7-24% mortality as compared to 50-80% in those with co-morbid conditions and/or multiple organ failure [21-22]. It also increases with number of failed organs both in and out of intensive care unit settings [23]. It is tempting to conclude from this study that the cases complicated by septicemia had better outcome on dialysis than on conservative management but for the small number of patients and lack of information on the fate of those that absconded. This may not be surprising as these severe cases presented in high catabolic state that needed a high clearance technique which haemodialysis offered. The terminal event in the cases that died were overwhelming sepsis and severe azotaemia despite the use of safe potent antibiotics which suggest that it may be difficult to control sepsis in the setting of severe uraemia. Prognosis was generally good in this group of ARF due to nephrotoxins as the survival rate was 85%.

This is in accord with the studies of Adelekan *et al* [7], McMurray *et al* [23] and Adu *et al* [24] who reported survival rates between 75 and 85% but higher than 54% survival noted by Ojogwu [10] He however observed that six of the dead cases were over 50 years of age, had prolonged oliguria and hepatic failure [10]. In conclusion, ARF due to nephrotoxins is common in our environment, the toxins are potentially preventable and prognosis is better with dialysis therapy.

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