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Burden and Predictors of Amphotericin - B Induced Acute Kidney Injury (AKI) and Other Adverse Events among Kala - Azar Patients of North India - A Hospital Based Study.

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Abstract:
Background*: Kala - azar has been a serious medical and public health problem in India since historical times, caused by genus Leishmania and is transmitted by sandfly (Phlebotomus). The National Health Policy 2002 set the goal of Kala - azar elimination by year 2015.*
Method*: We conducted a hospital based prospective study. A total 150 patients selected on the basis of clinical findings and hemato-pathological confirmation of Leishmania. Acute kidney injury (AKI) during treatment with Amphotericine-B assessed by using values of serum Creatinine.*
Result: *Incidence of Acute Kidney Injury reported to be 32 percent. Female patients reported higher rate 37.2 per cent as compared to 26.4 per cent among male patients.*
Discussion: *We assessed the burden of disease and explored the predictors of AKI among Kala - azar patients receiving Amphotericin - B. We recommend other forms of Amphotericin - B like Liposomal Amphotericin B and combination therapy of drug like Miltefosine and Paramomycin.*
Conclusion: *The study population has high burden of AKI with an overall incidence rate of 32 percent with a female preponderance. The study has implications for clinicians involved in care of Kala - azar in endemic areas of world.*

I. Introduction

History of Kala - azar is much older than any documented record. Twining writing in 1835 described a condition that he called Endemic cachexia of tropical countries that are subject to paludal exhalation. Word kala (black) and azar (fever) i.e fever overloaded with dark complexion in other hindi meaning it may called as fatal illness. Burdwan fever, Dr French (1854-75), the civil surgeon of Burdwan. He observed a contagious fever with enlargement of spleen, diarrhea, anasarca , Hepatomegaly in some patients. Harold Brown investigating "kala - dukh" in Purnia district of Bihar-similar as kala-azar of Assam.

Leishman reported two discovery as early as 1900 , of peculiar bodies in the spleen pulp of a soldier who died of Dum-Dum fever at Netely Hospital, Later on he published his work in British Medical Journal in 1903 "on the possibility of the occurance of Trypanosomias in India".

In July 1903, Donovan reported the finding of similar bodies from the spleen of patients suffering from prolonged fever with spleenomegaly in Madras (now Chennai). Hence contested Leishman view that they were degenerate trypanosomes.

Rogers(1904) published a paper "Leishman-Donovan Bodies in malarial cachexia and Kala - azar " described development of parasite of cachexial fever and kala-azar on to a flagellate stage- Kala - azar of Assam and many cases of so called- "Malarial cachexia" were one at the same diseases.[1]

Brahmchari (1906) described Kala-azar in his paper on a contribution to the study of fever due to Leishman Donovan bodies .

Kala - azar is a slow progressive Indigenous disease caused by genus Leishmania and primarily infect the Reticulo endothelial system with a fatality rate as high as 100 per cent within two years if untreated.[2] It is transmitted by sandfly (Phlebotomus) found commonly in crevices of mud walls and its range of flight is limited.

In 1970 Bihar province in India experienced a massive epidemic of Kala - azar (Visceral leishmaniasis) and the disease is still endemic in some areas . Out of 400000 new cases of leishmaniasis in the world in 1977 , a quarter occurred in Bihar. Sodium Stibogluconate was used ad first line drug during this epidemic.[3]

Concerned with the increasing problem of Kala - azar in country the Government of India launches a centrally sponsored Kala - azar Control Programme in endemic states of country in 1990 - 91. The National Health Policy - 2002 set the goal of Kala - azar elimination by 2015. In India Sodium Stibogluconate is used as first

line drug but due to high resistance to the first line drug, Amphotericin - B is being used as first line drug in tertiary care hospital of endemic states in India.[4]

II. Material and Methods

Bihar is 13th largest state in india by area (94,163 sq kilometers) and 3rd largest state by population (103,804,637) (2011 census) and has network of 18535 Sub centers, 3083 Primary Health Centers, 770 Community Health Centers, 9 Medical College & Hospital, and one AIIMS.

Sri Krishna Medical College & Hospital is a 500- bedded government medical college located in the town of Muzaffarpur which is about 80 kilometers from the capital city Patna of the state Bihar, India. Since Kala - azar is endemic in the town of Muzaffarpur, the hospital is usually considered the ideal place for provision of care to Kala - azar patients. Amphotericin B is provided as the initial treatment for patients who are admitted in the Institute.

Study Population

All the patients diagnosed with the Kala -azar and provided treatment in the indoor setting formed the study population for current study. We intend to generalize our finding to kala - azar patients provided Amphotericin B in the setting of indoor department of tertiary care hospital. Patients who were diagnosed with actual identification of Leishman donovani amastigote form (LD bodies) through either splenic puncture or bone marrow aspirations or the other sources was considered to be a case of Kala – azar.

Patients who received at least one dose of Amphotericin B was eligible for study even if the complete course of the drug was not provided. Amphotericine B was given as slow infusion with Dextrose containing fluid at a maximum dose of 1 mg/Kg body weight. We also intended to find the reason for discontinuation of full- therapy such as death of the patients if severe adverse reactions or patients leaving the hospital without information (Left Against Medical Advice-LAMA). Patients for whom information on serum creatinine is not available at baseline and during treatment was excluded from the study.

Definition used-

A case of Kala - was defined as a person from an endemic area with fever of more two weeks duration and with splenomegaly, who is confirmed by an Rapid Diagnostic Test or a biopsy (by splenic puncture or bone marrow aspirations) to find LD bodies in the smear. Acute Kidney Injury (AKI) was defined as at least 1.5-2 times increase in the level of serum creatinine during treatment as compared to baseline value as per RIFLE Criteria.[5]

Sample Size-

At 95 per cent confidence limit, 10 % absolute precision and anticipated 15 % non-response on account of the incomplete medical records and refusal from patients, thus a final size of 150 patients was considered for our study.

Study Instrument-

We developed a structured study instrument to collect information on selected socio - demographic and economic variables of the patients, base line medical history at the time to the ward, course of illness during stay in hospital, Biochemical parameters such as serum creatinine level to identify Acute Kidney Injury and other adverse effects of the drugs. Information was also collected from the records of the patients available in the Medical Records Department for past cases and from patients and clinicians for prospective cases.

Statistical Analysis-

Data was entered on Microsoft Excel and analyzed using SPSS versions 21. For counts, we reported proportion with confidence intervals. For continuous data, we reported mean with standard deviation (or median with intetquartile range for skewed data). We calculated incidence rate of Acute Kidney injury. We applied Chi-square test for bivariate analysis using linear or logistic regression.

Ethical Approval-

Ethical approval was obtained from the Institutional Ethical Committee (IEC) of the Institute. Written informed consent was obtained from the study participants and all data were maintained confidential. Appropriate medical and referral care were offered to the patients as needed during study. Only the research team has access to the information collected. During data- analysis and report writing all personal identifiers were removed such as name, address and phone number etc.

III. Results

A total of 150 patients with confirmed diagnosis of Kala-azar were enrolled for the study. (Table 1)

Table-1 Data Collection Details

S No	Parameters	Number
1	Number of patients approached	150
2	Patients eligible for study	150
3	Consent refused	0
4	Data collection completed	150
5	Complete data base available	150

Response Rate- A total of 100 Patients completed the response detail and educational status.

Table-2 Response Details-

S No	Parameters	Number (%)
1	**Type of respondent**	
1.1	Self	87 (58)
1.2	Relatives	63 (42)
1.3	Others	0
2	**Educational Status of Respondent**	
2.1	Able to read & write in any language with understanding	31 (34)
2.2	Mean years of schooling completer by respondent	2.5 years (37)

Table 3- Socio - demographic characteristics of patients (n=150)

S No	Parameters	Male (%)	Female (%)	Total
1	Sex	72 (48)	78 (52)	150 (100)
2	**Religion**			
2.1	Hindu	67 (93.1)	69 (88.5)	136 (90.7)
2.2	Muslim	5 (6.9)	9 (11.5)	14 (9.3)
2.3	Christian s	0	0	0
2.4	Sikhs	0	0	0
2.5	Others	0	0	0
3	**Socio - economic status**			
3.1	Middle & higher Income	7(9.7)	5 (6.4)	12 (8)
3.2	Lower Income	65 (90.3)	73 (93.6)	138 (92)
4	Mean per capita family Income (in Rupees)	3223.3 (1544.8)	2665.7 (1833.1)	2993.4 (1718.1)
5	Mean age (±SD)	36.9 (±12.5)	33.3 (±11.1)	35.1 (±11.9)
5.1	**Age groups**			
	<18 years	4 (2.9)	8 (2.6)	12 (2.7)
	≥18 years	68 (97.1)	74 (97.4)	142 (97.3)
6	Mean family size (±SD)	5.6 (±1.8)	5.4 (±1.8)	5.5 (±1.8)

Table-4 Incidence of Acute Kidney Injury (AKI) (n=150). Acute kidney injury as calculated by rise in serum creatinine level. (Figure 1)

S No	Parameters reported	Male (%)	Female (%)	Total (%)
1	Physician diagnosed AKI	0	0	0
2	AKI as per RIFLE criteria	19 (26.4)	29 (37.2)	48 (32)
2.1	Mean creatinine baseline in mg/dl (± SD)	0.70 (±0.25)	0.72 (±0.65)	0.71 (±0.5)
2.2	Mean creatinine mid treatment in mg/dl (±SD)	0.83 (± 0.26)	0.84 (±0.25)	0.83 (±0.25)
2.3	Mean creatinine end treatment in mg/dl (±SD	0.95 (±0.31)	0.96 (±0.32)	0.96 (±0.32)
3	Patients with HBsAg positive	0	0	0
4	HIV positive patients	0	1 (1.3)	1 (0.7)

Figure 1. Mean Sreum Creatinine level in mg/dl during treatment with Amphotericine B.

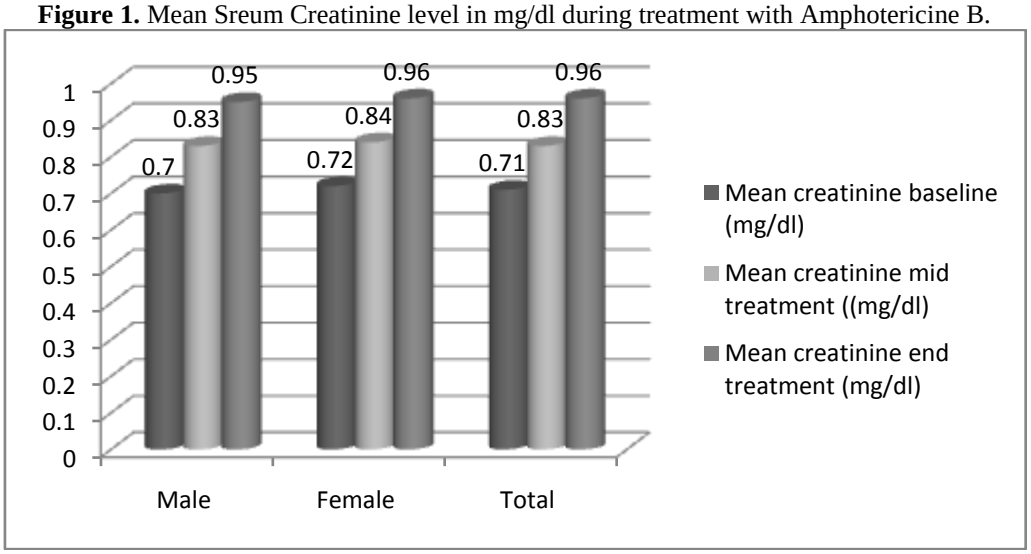

Table 5-Associated preadmission symptoms of patients diagnosed with Kala azar (n=150). Graphically represented in Figure 2.

S No	Parameters reported	AKI present	AKI absent	Total
A	**Symptoms**			
1	Fever	48	102	150
2	Loss of appetite	48	102	150
3	Fatigue/weakness	48	101	149
4	Burning sensation during urination	8	11	19
5	Cold	15	24	39
6	Cough	0	0	0
7	Loose stool	14	25	39
8	Vomiting	6	11	17
9	Vertigo	5	16	21
10	Loss of body weight	39	75	114
11	Mean loss of body weight	0	0	0
12	Blackish pigmentation on forehead	2	2	4
13	Perioral blackish pigmentation	0	1	1
14	Blackish pigmentation on temporal area	0	0	0

Figure 2. Associated symptoms in patients with Kala azar (n =150)

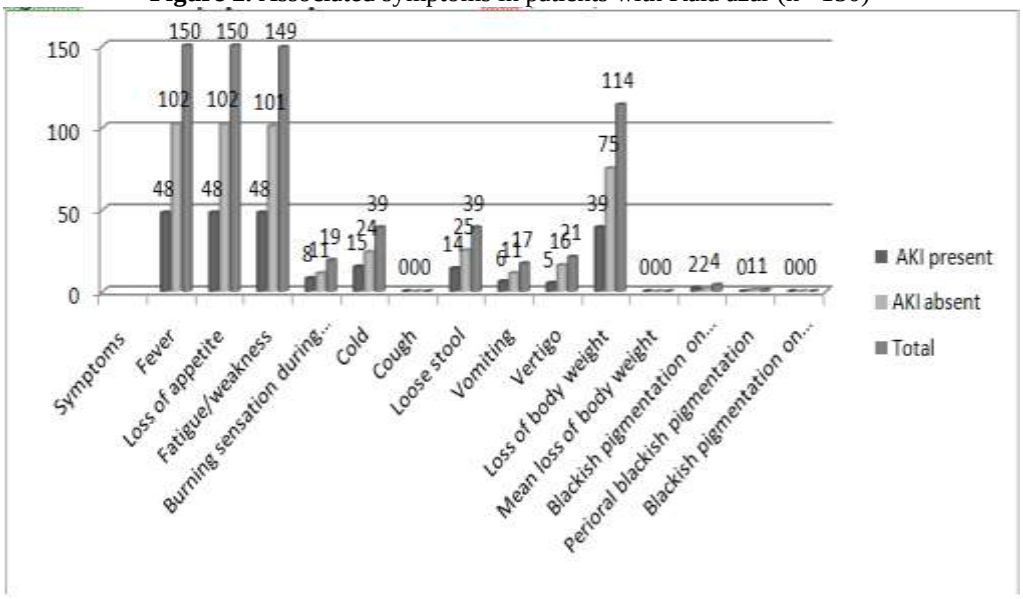

Table 6- Association of observed sign in patients with Kala azar (n = 150). On general and specific examination of the patients by the physician. (Figure 3)

S No	Parameters reported	AKI present	AKI absent	Total
1	Pallor	26	28	54
2	Icterus	2	0	2
3	Clubbing	0	0	0
4	Cyanosis	0	0	0
5	Oedema	3	3	6
6	Koilonychia	0	0	0
7	Lymphadenopathy	0	0	0
8	Alopecia	3	17	20
9	Blacish pigmentation	0	0	0
10	Spleenomegaly	48	102	150
11	Hepatomegaly	46	101	147
12	Weight loss(from medical records)	36	65	101
13	Decreased urine	3	5	8
14	Facial puffiness	5	5	10

Figure 3. Obsereved signs in patients with Kala azar.

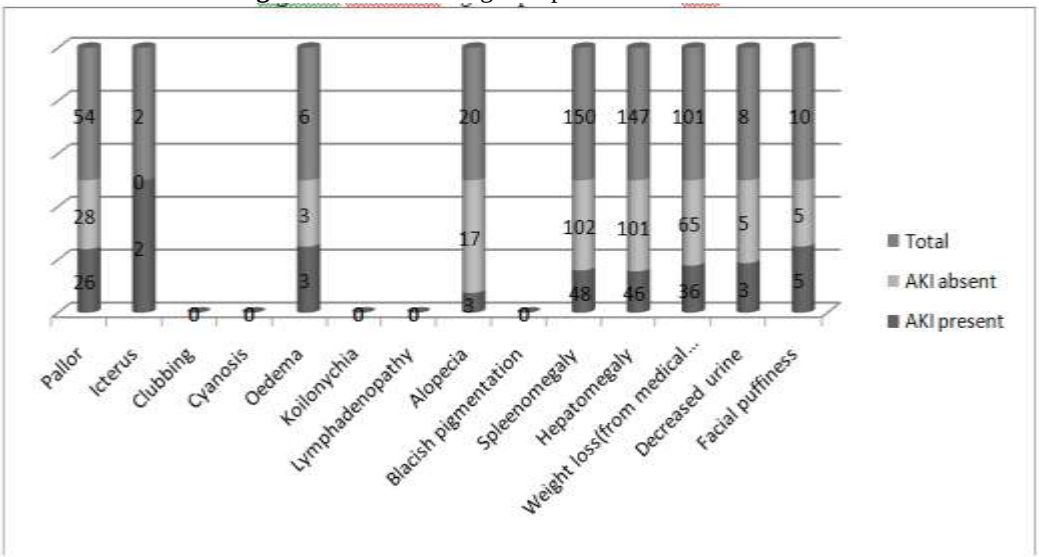

Table 7- Association of previous drug treatment with AKI (n = 150)

S No	Parameters reported	AKI present (%)	AKI absent (%)	Total
1	Chloroquine	1	0	1
2	Quinine	1	2	3
3	Artemesin	4	2	6
4	Artether	4	2	6
5	Artmether	4	2	6
6	Cephalosporins	3	2	5
7	Fluoroquinolones	4	2	6
8	Cotrimoxazole	3	1	4
9	Anti-tubercular drugs	2	2	4

Table 8-Association of patient level personal risk factors with AKI (n = 150)

S No	Parameters reported	AKI present	AKI absent	Total
1	Tobacco-smoking(cigarette, bidi)	5	9	14
2	Tobacco-smokeless (Khaini, zarda, gutkha	10	21	31
3	Alcohol	9	18	27
4	Bhang/ganja	1	5	6

Table 9-Association of patients level medical risk factors with AKI (n = 150).

S No	Parameters reported	AKI present	AKI absent	Total
1	Human Organ Transplantation	0	0	0
2	HIV	0	1	1
3	Hepatitis B	0	0	0

4	Bypass surgery	0	0	0
5	Hypertension	0	0	0
6	Diabetes mellitus	0	0	0
7	Chronic Kidney disease	0	0	0

Table 10-Association of environmental risk factors with AKI (n = 150)

S No	Parameters reported	AKI present (%)	AKI absent (%)	Total
1	Mud walls	35	69	104
2	Cattle Dung	17	27	44
3	Mosquito Net during sleeping	0	2	2
4	Stagnant water near house	7	20	27
5	Screen in windows/doors of house	5	18	23

Table 11-Association of various family level risk factors with AKI (n = 150)

S No	Parameters reported	AKI present	AKI absent	Total
1	Family member diagnosed with Kala - azar recently	13	7	20
2	Family member known to have HIV	1	0	1
3	Family with h/o of Hepatitis B	0	1	1
4	Family with h/ o of Diabetes mellitus	3	8	11
5	Family with h/o of Hypertension	4	6	10
6	Family with h/o of Kidney disease	0	0	0

IV. Discussion

We have reported the assessment of burden and explored the predictors of Acute Kidney Injury among Kala - azar patients receiving Amphotericin - B at a tertiary care hospital of north India. The reported incidence of Acute Kidney Injury (AKI) using the RIFLE criteria was reported to be overall 32 % with a female preponderance.

We recommend routine use of renal function test among Kala - azar patients receiving Amphotericin B treatment to predict the risk of AKI . Patients devolping AKI during treatment thus can be easily monitored and appropriate action can be taken.

V. Conclusion

The study population has a high burden of AKI with an overall incidence rate of 32 percent with a female preponderance. The study has implications for clinicians involved in care of Kala - azar in endemic areas of the world. The considerable burden of AKI among this group of patients should be further explored for its relation with risk of mortality.

Conflict of interest –Nil

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