ORIGINAL ARTICLE

OBSERVATION ON TOXICITY OF INTRAVENOUS AMPHOTERICIN-B IN DIAGNOSED CASES OF KALA-AZAR IN DAILY VERSUS ALTERNATE DAY REGIMEN

Vishal Parmar[1], Rakesh Kumar[2], Mehre Darakhshan Mehdi[3], Pramod Kumar Agrawal[4], Yadu Nath Giri[5]

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ABSTRACT: Visceral leishmaniasis (Kala-azar) is a disease caused by a protozoan parasite, Leishmaniasis donovani and transmitted by the bite of sand fly vector Phlebotomus argentipes. For patients with Indian visceral leishmaniasis, Amphotericin-B deoxycholate is usually given as 15 alternate-day infusion of 0.75mg/kg over 30 days; daily treatment with 0.75mg/kg body weight is also used. An observation of toxicity of intravenous Amphotericin-B in diagnosed cases of Kala-azar on daily versus alternate day regimen on a dose of 0.75mg/kg body weight was compared. Results revealed that daily regimen of Amphotericin-B in a dose of 0.75 mg/kg body weight can be given safely to patients and this regimen can not only reduce the financial burden on the patients but can also reduce hospital stay.
KEYWORDS: Kala-azar, Amphotericin-B, Daily, Alternate day, Regimen.

INTRODUCTION: Visceral Leishmaniasis (VL) or Kala-azar is a disease caused by a protozoan parasite, Leishmania donovani and transmitted by the bite of the female sand fly vector Phlebotomus argentipes. It occurs in more than 80 countries of Asia, Africa, Southern Europe and South America, with a total of 200 million people at risk.[1,2] However 90% of the estimated 500,000 new symptomatic cases per year occur in just five countries: India, Sudan, Bangladesh, Nepal and Brazil.[3] India contributes to about 40%-50% of the world's cases, from which 90% are from Bihar State alone. Kala –azar remains a serious public health problem in Bihar.[4] The rising trend of unresponsiveness to sodium stibogluconate (SSG) in Bihar has been reported as 35%-45%. This has resulted in loss of affordable drugs and forced the clinicians to use alternative antileishmanial drugs.[5–7]

Amphotericin-B (AMB) is used extensively in Sb^v refractory patients in Bihar as infusion in doses of 0.75-1.0 mg/kg on alternate days, and 15-20 infusions cures more than 98% patients.[8] Present reviews advocate AMB as a first-line drug in the treatment of both unresponsive and fresh cases of Kala-azar.[9] Further reviews reveal a cure rate of about 96%-97%, at the six month in either daily or alternate day infusions.[9,10]

Much toxicity has been attributed to Amphotericin-B. Major acute reactions to drug are fever, chills, rigor, malaise, nausea, vomiting, anorexia and body aches. Sometimes hyperapnoea, respiratory stridor and hypotension may occur but bronchospasm and anaphylaxis is rare. The most troublesome side effect of AMB therapy is nephrotoxicity. Up to 80% of patients treated with AMB will experience an episode of altered renal function.[11]

AMB is reported to cause a decline in glomerular filtration rate (GFR), renal tubular acidosis, decreased serum potassium, and diminished renal concentrating ability. The decrease in GFR appears to be related to decrease in renal blood flow leading to cortical ischaemia. AMB induced renal tubular acidosis is characterized by hypokalaemia, and inability to excrete an acid load and occasional nephrocalcinosis, generally without induction of systemic acidosis.[12] AMB can severely depress red cell production, resulting in normochromic, normocytic anaemia. The anaemia is usually reversible upon discontinuation of therapy, with a return of haematocrit to pre-treatment levels within several months.

The present study was done for the observation of toxicity of intravenous Amphotericin-B in diagnosed cases of Kala-azar on daily versus alternate day regimen ona dose of 0.75mg/kg body weight.

MATERIALS AND METHODS: The present study was conducted on diagnosed cases of Kala-azar admitted in indoor wards of Department of Medicine, Katihar Medical College and Hospital, Katihar. The study was carried out for a period of one year which was pre-approved by the Ethical Committee of this institution. All the patients were subjected to detailed history taking and clinical examination. Pregnant women, lactating women, HIV sero positive individuals and patients with associated diseases like Tuberculosis, Malaria, Diabetes and Hypertension were not included in the study. Exclusion criteria also included the following finding: Hb <3.5 g/dl, platelet count <50,000/mm^3, leucocyte count <2000 cells/mm^3, serum creatinine >2.0 mg/dl, abnormal liver function test and patient who had past history of Kala-azar in the last five years. Out of ninety-one participants who were enrolled for the present study with age ranging from 10 to 65 years, fifty fresh diagnosed cases of Kala-azar was selected for the study. They were randomly divided in two groups of 25 each.

Group A - of 25 patients received amphotericin-B in a dose of 0.75mg/kg body weight for 15 infusions.
Group B - patients received amphotericin-B in a dose of 0.75mg/kg body weight on alternate days for 15 infusions.

Treatment started within 24 hours of diagnosis of Kala-azar by examination of splenic/bone marrow aspirate specimens and all patients received test dose of 5mg AMB. Patients were kept in our inpatient medicine units throughout the treatment period and were examined daily. Complete blood cell count, serum creatinine, Blood urea nitrogen (BUN), Serum potassium were determined on day 1, day 8 and day 15 of Group A, While Group B on day 1 day 8, day 15 and day 30. An additional splenic or bone marrow aspirate specimens were obtained for apparent cure evaluation one day after treatment ended. Parasitic density score for pre and post-treatment aspirate were graded microscopically.

Statistical analysis: The paired t test was used to compare pre and post treatment values in each group, while unpaired t test was used for comparing changes in different parameters of each group. A p value of <0.05 was considered to be statistically significant.

OBSERVATION: In this study, we compared the two groups namely Group A and Group B on different parameters. The clinical and laboratory characteristics of the patients of both the treatment groups were compared (Table 1). Leucocyte count, haemoglobin, BUN was significantly comparable. Other parameters shows varying degree of significance which may attribute to small sample size.

Parameters	Group A (Mean±SD)	Group B (Mean±SD)	P value
Weight (in kg)	51.56 ± 11.47	49.26± 8.52	0.4249
Spleen (in cms)	4.2 ± 1.15	4.30 ± 1.20	0.7648
Liver (in cms)	1.06±1.03	1.00±0.95	0.8314
Leucocyte count	4468±932.61	5332±1374.08	0.0123[a]
Haemoglobin (mg/dl)	6.17±1.43	7.64±1.93	0.0036[a]
BUN (mmol/l)	11.85±2.83	10.22±2.45	0.0344[a]
Serum creatinine (mg/dl)	0.84±0.16	0.85±0.17	0.8313
Serum potassium (mg/dl)	4.75±0.41	4.51±0.51	0.0729

Table 1: Clinical and laboratory characteristics on Day 1

a = significant value, SD = standard deviation

	GROUP A n = 25			GROUP B n = 25		
Characteristics	**DAY 1**	**DAY 15**	**P VALUE**	**DAY 1**	**DAY 30**	**P VALUE**
Weight (kg)	51.56±11.47	52.06±11.32	0.0001	49.26±8.52	50.12±8.48	0.0126
Spleen size (cms)	4.2±1.15	0.76±0.72	0.0001	4.30±1.20	0.74±0.75	0.0001
Liver SIZE (cms)	1.06±1.03	0.12±0.33	0.0001	1.00±0.95	0.00±0.00	0.0001
Leucocytes counts (cells/ mmcu)	4468±932.61	6784±942.81	0.0001	5332±1374.08	9332±880.2	0.0001
Haemoglobin (gm/dl)	6.17±1.43	7.54±1.27	0.0001	7.64±1.93	9.33±1.73	0.0001
BUN (blood urea nitrogen) levels (mg/dl)	11.85±2.83	17.33±1.88	0.0001	10.22±2.45	15.75±2.36	0.0001
Serum creatinine (mg/dl)	0.84±0.16	1.56±0.20	0.0001	0.85±0.17	1.08±0.21	0.0001
Serum potassium (mg/dl)	4.75±0.41	4.13±0.44	0.0002	4.51±0.51	4.18±0.33	0.1435[b]

Table 2: Baseline and post treatment clinical and laboratory data

b = p value not significant, SD = standard deviation

Table 2 shows a very significant improvement of Weight, Leucocyte count, Haemoglobin concentration ($p<0.0001$) but significant increase of BUN and creatinine concentration levels too ($p<0.0001$) in both treatment groups when compared with day 1 of treatment commencement. Similarly, There was significant regression of splenic and liver size seen ($p<0.0001$). Serum potassium decreases in both treatment groups when compared with day 1 levels.

Table 3: Showing grading of LD bodies (No. of LD bodies per 1-1000 fields) in splenic/bone marrow aspirate before, during and completion of treatment in both groups.

Days of observation during treatment	GROUP A, n = 25 L.D bodies (No./ 1-1000 fields) Mean ± SD	GROUP B, n = 25 L.D bodies (No. / 1-1000 fields) Mean ± SD
DAY 1ST	3±1	3±1
DAY 8TH	1.3±0.7	
DAY 15TH	0±0	1.3±0.7
DAY 30TH		0±0

Table 3 shows L. D bodies (No./1-1000 fields) found in splenic/bone marrow aspirate in Group A and Group B . It reveals similar pattern of parasitic density clearance in both groups. Group A day 1, day 8 and day 15 parasitic densities were same as Group B day 1, day 15, and day 30.

	Group A	Group B
Clinical cure	100%	100%
Parasitological cure	100%	100%

Table 4: Showing comparison of cure among patients of Group A and Group B

Cure was similar (i.e. 100%) in both groups of patients.

Table 4: Shows clinical and parasitological cure rate of both treatment groups is same and 100%.

S. No.	Parameters	Group A (MEAN ± SD)	Group B (MEAN± SD)	P value
1	WEIGHT (kg)	0.5±0.38	0.86±0.53	0.0082C
2	SPLEEN (cms)	3.44±1.04	3.56±1.04	0.6851
3	LIVER (cms)	0.96±0.97	0.94±0.89	0.9398
4	LEUCOCYTE COUNT (cmm)	2316±624.28	4000±892.56	0.0001C
5	HAEMOGLOBIN (gm%)	1.36±0.37	1.64±0.68	0.0768
6	S.CREATININE (mg/dl)	0.31±0.25	0.23±0.21	0.2265

7	BUN (mg/dl)	5.47±3.33	5.53±3.19	0.9482
8	S.POTASSIUM (mg/dl)	0.62±0.69	0.32±0.61	0.1099

Table 5: Shows comparison with baseline (day 1) data, to post treatment data. Demonstrated significant increase in weight and total leucocyte count ($p<0.05$)

c = significant value, SD = Standard Deviation

Table 5: Demonstrated significant increase in weight and total leucocyte count ($p<0.05$).

DISCUSSION: There were ninety one participants initially enrolled for the study, out of which 41 were excluded due to non-adherence to inclusion and exclusion criteria. 50 confirmed Kala-azar cases were randomly divided into two groups of 25 each, namely Group A (daily dose of 0.75mg/kg body weight for 15 infusion) and Group B (alternate day dosing of 0.75 mg/kg body weight for fifteen infusions). The clinical and laboratory characteristics of the patients of both the treatment groups were compared (Table 1), before initiation of treatment. During the therapy, clinical and parasitological response, adverse effects and toxicities were closely monitored. In the present study, fever with chills was observed equally in both groups, during first week of therapy. The incidence of anorexia and vomiting was observed more in Group A than Group B patients. There was increase in BUN and serum creatinine during the course of therapy although it did not cross the normal limits and was not a problem to warrant stoppage of therapy. There was significant rise of BUN and serum creatinine in two treatment groups ($p<0.0001$) (Table 2). Fall in potassium level was observed in some patients in both the groups. Its incidence was higher in group B patients than in group A. It was corrected by oral potassium supplement and did not cause concern. Splenic and liver regression and weight gain after treatment completion was very significant ($p<0.0001$) in both treatment group when compared with day 1 (Table 2). Similarly, leucocyte count and Haemoglobin improvement were seen significantly ($p<0.0001$) in both treatment groups during and completion of treatment. Table 3 shows L.D bodies (No. /1-1000 fields) found in splenic/bone marrow aspirate in Group A and Group B. It reveals similar pattern of parasitic density clearance in both groups. Group A day 1, day 8 and day 15 parasitic density was same as Group B day 1, day 15, and day 30. while, Table 4 shows Clinical and parasitological cure rate of both treatment group is same and 100%. Table 5 shows comparison with baseline (day 1) data, to post treatment data demonstrated significant increase in weight and total leucocyte count ($p<0.05$) in both treatment groups. Other parameters shows varying degree of significance which may have attributed to small sample size. Although the Amphotericin-B deoxycholate is associated with longer duration of treatment and other toxicities in comparison to lipid formulation and lipid formulations are superior in these terms,[13,14,15] high cost has rendered these effective agents largely irrelevant in the Indian subcontinent. The efficacy of AMB and its lipid formulation was found equally effective[16] whereas the efficacy of AMB lipid formulation was found as 100%[17] which further declined to 92% in a study conducted in 2007.[18] By comparing treatment outcome, toxicity and adverse effects of drug in both treatment groups we can conclude that daily treatment, allowing for a shorter duration of hospitalization, is particularly relevant in an impoverished region where hospital beds are at a premium and long inpatient stays

equate importantly with lost wages and appreciable family life disruption. Thus present study observed no sufficient toxicity to warrant withdrawal of the drug, whether Amphotericin-B was given daily or on alternate days. Both the dose schedules had been observed in the present study to be equally effective and safe, however, daily dose schedule has been observed in the present study to require 15 days lesser hospital stay than alternate day therapy. Therefore Amphotericin-B in a dose of 0.75 mg/kg body weight can be given safely to patients and this regimen can not only reduce the financial burden on the patients but can also reduce hospital stay.

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AUTHORS:

1. Vishal Parmar
2. Rakesh Kumar
3. Mehre Darakhshan Mehdi
4. Pramod Kumar Agrawal
5. Yadu Nath Giri

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Medicine, Katihar Medical College, Katihar, Bihar.
2. Assistant Professor, Department of Medicine, Katihar Medical College, Katihar, Bihar.
3. Assistant Professor, Department of Pharmacology, North Bengal Medical College, Darjeeling, West Bengal.
4. Professor & Head, Department of Medicine, Katihar Medical College, Katihar, Bihar.
5. Professor, Department of Medicine, Katihar Medical College, Katihar, Bihar.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Vishal Parmar,
Associate Professor,
Department of Medicine,
Katihar Medical College,
Katihar – 854105, Bihar.
E-mail: vpktr123@gmail.com

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