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Comparison of Toxicity of Intravenous Amphotericin B in Diagnosed Cases of Kala Azar on Daily versus Alternate Day Regimen

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Abstract
Introduction: *Kala- azar (visceral leishmaniasis) is a disease caused by unicellular eukaryotic obligatory intracellular protozoa of the genus Leishmania and primarily affects the host's reticuloendothelial system. The organisms are transmitted by phlebotomine sandflies of the genus phlebotomus. Amphotericin B deoxycholate is first line drug treatment of kala-azar in endemic regions of Bihar and given as 15 alternate day infusion in a dose of 1 mg/kg over 30 days; however daily regimen of 1 mg/kg can also be used over 15 days. The aim and objectives of the study is to compare the toxicity of intravenous Amphotericin B if any, in diagnosed cases of kala-azar on daily versus alternate day regimen.*
Materials and Methods: *The present study was conducted on 60 freshly diagnosed cases of kala-azar. All patients above 10 years of age of either gender with a diagnosis of kala-azar were included in the study. They were divided randomly in two groups each having 30 patients. Group A patients received AMB in a dose of 1mg/kg for 15 infusions over 15 days while Group B patients received it in a dose of 1mg/kg as 15 alternate day infusion over 30 days. The results of various parameters were recorded during treatment and then weekly to assess the response of therapy. The pretreatment record of investigations formed the basis of reference of toxicities, if any.*
Results: *Out of 60 cases of kala-azar 37(61.66%) were male and 23(38.33%) were female. 66.66% of total kala-azar patients were young and found in the age group of 11-30 years. The characteristics like average weight gain, the regression of size of spleen and liver, haemoglobin and total leucocyte count were found to be significant (p value<0.05) in both treatment groups.*
Conclusion: *The results of the study reveals that daily regimen of Amphotericin B in a dose of 1 mg/kg body weight can be given safely to kala-azar patients and this regimen cannot only lessens the financial burden of the patients but can also minimizes the hospital stay.*
Keywords: *kala-azar, Amphotericin B, Alternate day, Daily, Regimen, Toxicity.*

Introduction

Leishmaniasis is a group of protozoal diseases caused by parasite of the genus leishmania and transmitted from one person to another by the bite of female phlebotomus sandfly.[1] They are responsible for various syndromes in human- Kala-azar, cutaneous leishmaniasis, mucosal leishmaniasis, and post kala azar dermal leishmaniasis etc. The Kala-azar is still most important disease of this group. It is also known as Visceral leishmaniasis, Dumdum fever, Burdwan fever, Sirkari disease or Black fever. The sensitivity of splenic aspirate smear is found to be greater than 90% and is regarded as the gold standard for the diagnosis of kala-azar.[2,3,4]

In India it has its home in plains of the Ganges and the Brahmaputra. It has assumed epidemic proportion in Bihar mostly in the districts which belongs to north Bihar.[5]

Sodium stibogluconate is the first line drug treatment of Kala-azar but in India specially in Bihar where disease is endemic, Amphotericin B and various lipid formulations of it is used as the first line drug for the treatment of Kala-azar.[6] The recommended dose of Amphotericin B is 0.75 – 1.0 mg per kg body weight on alternate days for a total of 15 infusions.[7] Amphotericin B is highly toxic and is reported to have many toxicities so its various lipid formulations can be used which have minimal side effects.[8,9,10]

Acute toxicities of Amphotericin B are commonly observed and are infusion related and consists of chills, rigor, fever, aches and pains, nausea, vomiting, anorexia, dyspepsia and thrombophleb-itis at the site of infusion.[11] Long term toxicity of Amphotericin B is dose related and also depends on the duration of therapy.[9] Nephrotoxicity is the most important. The manifestations are azotemia, reduced glomerular filtration rate, renal tubular acidosis with renal wasting of potassium and magnesium which may result in hypokalemia which when acute and severe occasionally lead to cardiac arrest or ventricular arrhythmia. Other rare toxicities are bone marrow depression leading to anemia, thrombocytopenia, and mild leukopenia.

The present study was undertaken to observe whether Amphotericin B is toxic in the dose of 1 mg per kg body weight daily and to compare its toxicities, if any on daily versus alternate day dose schedule.

Materials and Methods

The present cross sectional comparative study was conducted on sixty freshly diagnosed cases of kala-azar admitted in indoor ward of Department of Medicine, Patna Medical College and Hospital, Patna, Bihar. Duration of study was one year. All patients above 10 years of age of either gender with a diagnosis of kala-azar were included in the study. They were randomly divided into two groups of thirty each. Group A of 30 patients received Amphotericin B in a dose of 1.0 mg per kg body weight daily for 15 days and Group B of another 30 patients received Amphotericin B in a dose of 1.0 mg per kg body weight on alternate days for a total dose of 15 mg per kg. Patients below 10 years of age and with cardiac, pulmonary, renal or with hepatic impairment were excluded from the study. Exclusion criteria also included pregnant and lactating women, HIV seropositive individuals and patients with associated diseases like tuberculosis, malaria, diabetes, hypertension, haemoglobin < 3.5 g/dl, platelet count < 50,000/cmm, WBC count <2000 cells/cmm, serum creatinine > 2mg/dl and patients who had past history of kala-azar in the last five years. All the selected patients were enquired in detail about the history of illness, thoroughly examined clinically for all systems and investigated for confirming diagnosis and to rule out any other co-existing illnesses.

Diagnosis of kala-azar was confirmed by demonstration of leishmania Donovan bodies in splenic or bone marrow aspirates. Normal coagulation profile was established by a normal platelet count, bleeding time, clotting time and prothrombin time prior to invasive procedure. At the start of therapy parasitological diagnosis was confirmed and graded according to number of leishmania Donavan bodies per 1000 microscopic

field as given below. Grading was assessed weekly during treatment.

Grading of leishmania donovani amastigotes in splenic/bone marrow aspiration smears.[12]

Grade	Average parasite density
0	Nil per 1000 microscopic fields
1+	0-1 per 1000 microscopic fields
2+	1-10 per 100 microscopic fields
3+	1-10 per 10 microscopic fields
4+	1-10 per microscopic fields
5+	10-100 parasites per microscopic fields
6+	>100 parasites per microscopic fields

Serum sodium, serum potassium, blood urea, serum creatinine, serum bilirubin, SGPT, plasma glucose both fasting and post prandial, CBC, chest x-ray PA view, ECG, urine analysis and fundoscopy were done and results were recorded during treatment and then weekly to assess the response of therapy. The pre treatment record of investigations formed the basis of reference of toxicities, if any. At the beginning of treatment all of the patients were assessed clinically for gain in weight, splenic index (splenic size in cms), state of appetite, size of liver in cms (along midclavicular line from costal margin), improvement of pallor and weight gain. All clinical criteria were assessed at weekly intervals during treatment and at monthly intervals for six months after the cure for any possible relapse.

Data documented and analysed using statistical package for social sciences (SPSS) and Microsoft excel. To compare pre and post treatment values in each group, paired t-test was used, while unpaired t-test was used for comparing changes in various parameters of each group. A p value of <0.05 was considered significant statistically.

Results

Out of 60 cases of kala-azar, 66.66% of patients were young i.e. in age group of 11-30 years [table-1]. Out of total 60 patients of kala-azar 37(61.66%) were male and 23(38.33%) were found to be female [table-2]. Average weight gain in group A patients was 2.03 kg by the end of therapy and this trend continued i.e. weight gain was maintained during follow up. In group B patients average weight gain by the end of therapy was 2.75 kg and found to be significant ($p<0.05$) by the second week of therapy [table3,4]. The rate of regression of liver and spleen was significantly ($p<0.05$) more in group A patients as compared to group B patients [table-4], however none of the patients reported increase in liver and splenic size during follow up. Other parameters like haemoglobin and TLC were found significant ($p<0.05$) in both groups during and after completion of therapy. There was significant reduction in L.D. bodies grading by 8th day and 15thy day respectively in group A and group B patients and all patients were free from parasites by the end of therapy [table-5]. Table -6 shows clinical and parasiotological cure of patients of both groups at the end of treatment which was 100% in both treatment groups.

Table -1 Age distribution of patients of kala-azar

Age group	No.of cases	Percentage
11-20	20	33.33
21-30	20	33.33
31-40	9	15
41-50	5	8.33
51-60	6	10

Table-2 Sex distribution of patients of kala-azar

Sex	No. of cases	Percentage
Male	37	61.67
Female	23	38.33

Table-3 Clinical and laboratory parameters on Day 1 of kala-azar patients

S. No.	Parameters	Group A (mean ± S.D.)	Group B (mean ± S.D.)	P value
1.	Weight (kg)	51.56±11.47	49.26±8.52	0.4249
2.	Liver (in cms)	1.06±1.03	1.00±0.95	0.8314
3.	Spleen (in cms)	4.2±1.15	4.30±1.20	0.7648
4.	Haemoglobin (g/dl)	6.17±1.43	7.64±1.93	0.0036
5.	Total leucocyte count (cells/cmm)	4468±932.61	5332±1374.08	0.0123
6.	Serum potassium (meq/l)	4.75±0.41	4.51±0.51	0.0729
7.	Serum creatinine (mg/dl)	0.84±0.16	0.85±0.17	0.8313
8.	BUN (mg/dl)	11.85±2.83	10.22±2.45	0.0344

Table - 4 Baseline and post treatment clinical and laboratory data of kala-azar patients.

S .no	Parameters	Group A n=30			Group B n=30		
		Day 1	Day 15	P value	Day 1	Day 30	P value
1.	Weight (kg)	51.56±11.47	52.06±11.32	0.0001	49.26±8.52	50.12±8.48	0.0126
2.	Liver (cms)	1.06±1.03	0.12±0.33	0.0001	1.00±0.95	0.00±0.00	0.0001
3.	Spleen (cms)	4.2±1.15	0.76±0.72	0.0001	4.30±1.20	0.74±0.75	0.0001
4.	Hb (g/dl)	6.17±1.43	7.54±1.27	0.0001	7.64±1.93	9.33±1.73	0.0001
5.	TLC (cells/cmm)	4468±932.61	6784±942.81	0.0001	5332±1374.08	9332±880.2	0.0001
6.	Serum K^+ (meq/l)	4.75±0.41	4.13±0.44	0.0002	4.51±0.51	4.18±0.33	0.1435
7.	Serum creatinine (mg/dl)	0.84±0.16	1.56±0.20	0.0001	0.85±0.17	1.08±0.21	0.0001
8.	BUN (mg/dl)	11.85±2.83	17.33±1.88	0.0001	10.22±2.45	15.75±2.36	0.0001

Table -5 Grading of L.D. bodies (no. of L.D. bodies per 1-1000 fields) in Splenic/bone marrow aspirate before, during and completion of treatment in both groups of kala-azar patients.

Days of observation	Group A n=30 L.D. bodies no./1-1000 fields Mean ± S.D.	Group B n=30 L.D. bodies no./1-1000 fields Mean ± S.D.
Day 1st	3 ± 1	3 ± 1
Day 8th	1.3 ± 0.7	2 ± 1
Day 15th	0 ± 0	1.3 ± 0.7
Day 22nd	-	1 ± 0.2
Day 30th	-	0 ± 0

Table 6 Comparison of clinical and parasitological cure among kala-azar Patients of Group A and B.

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

Discussion

The present study "comparison of toxicity of intravenous Amphotericin B in diagnosed cases of kala-azar on daily versus alternate day regimen" was conducted on 60 diagnosed cases of kala-azar which were randomly divided into two groups of 30 each namely Group A (daily dose of 1mg/kg for fifteen infusions) and Group B (alternate day in a dose of 1 mg/kg for fifteen infusions). In our study two age groups i.e 11-20 and 21-30 had same number of patient's i.e 20 each. Thus maximum number of cases 40 (66.66%) was in the age group of 11-30 years and were young [table-1]. In this study the clinical and laboratory parameters of the included patients of both the treatment groups were analysed and compared before the initiation of the treatment [table-3]. During the treatment and after completion of the therapy, clinical, biochemical and parasitological response, adverse effects and toxicities were closely monitored. In the present study the mean body temperature of patients was found to be raised equally in both groups, during 1st week of therapy and touched the normal level by the beginning of 2nd week i.e 8th day of therapy and was maintained during follow up. Anorexia and vomiting was observed more in group A than group B patients. In the present study liver and splenic regression and weight gain after completion of therapy was very significant ($p < 0.0001$) in both group when compared with the day 1 i.e baseline [table -4]. The serum creatinine and BUN was found to be increased during the course of therapy however it did not cross the upper normal limit and was not an indication to stop therapy. Fall of serum potassium level was observed more in patients of Group B than in Group A; although it did not cause any problem and was corrected by oral potassium supplementation. Similarly improvement in haemoglobin and total leucocyte count were seen significant (p value <0.0001) in both groups during and after completion of therapy[table-4]. Other parameters shows varying degree of significance which may have attributed to small sample size. Table – 5 reports similar pattern of parasitic density clearance in both group A and group B. The present study also reveals that clinical and parasitological cure rate of both treatment group were same and was 100% [table-6].

Although the Amphotericin B deoxycholate is associated with longer duration of treatment and leads to toxicities in comparison to its several lipid formulations which are superior in these terms,[13,14,15] however high cost has rendered these effective agents in the developing Indian subcontinent. Also the efficacy of Amphotericin B

and its several lipid formulations was found to be equally effective.[16]

Conclusion

By comparing treatment outcome, adverse effects of the drug and toxicity in both treatment groups the present study accomplish that daily dose regimen, allowing a shorter duration of stay in hospital, is particularly relevant in necessitous region where hospital beds are not adequate and where long hospitalisation create a great financial burden and lost wages of parents. Thus present study observed no copius and dangerous toxicity to warrant withdrawal of the treatment, whether Amphotericin B was given daily or on alternate days regimen. Both the regimen schedules observed in this study is found to be equally safe and effective. Therefore Amphotericin B in a daily dose of 1mg/kg body weight can be given safely to kala-azar patients and this regimen schedule cannot only reduce the financial burden on the patients and his/her family members but can also reduce hospital stays.

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