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Original Article

Kala-azar in Children: A Retrospective Study

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Abstract

Fifty children with Kala-azar {27 male (54%) and 23 female (46%)} aged between 2-12 yrs, were studied retrospectively in the pediatric unit of Rajshahi Medical College Hospital to find out the optimal treatment of Kala-azar in children. Sodium stibogluconate was given intravenously at a dose of 10 mg/kbw/day for 20 days in one group (Group-A), 15 mg/kbw/day for 20 days in another group (Group-B), 10 mg/kbw/day B.D. for 20 days in another group (Group-C), and 20 mg/kg of body wt/day for 40 days is last group (Group-D). The apparent cure rates of all regimens were 100%. Side effects of sodium stibogluconate were mild, however, myocarditis developed on 37th day of treatment in one patient which reversed to normal after discontinuation of the drug. 27 patients (54%) could be followed up to six months after discharge from hospital. Two patients in group-A relapsed and none relapsed from group B, C or D. Follow-up of patients in group B, C and D showed improvement in general condition, increase in body weight, Hb% and regression of the size of the liver and spleen and ultimate rate of cure in B, C, D regimens were 100%. But ultimate cure rate in-group A was 71.4% and the significance of difference between A and other regimens (P<0.10) were statistically significant. Sodium stibogluconate 15mg/kg body weight once daily for 20 days (Group-B) had the best of cure rate with low toxicity and may be recommended for routine treatment of childhood Kala-azar in this country.

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Introduction

Kala-azar, also known as visceral leishmaniasis, is a parasitic disease, which is caused by *Leishmania donovani*, and transmission is carried out from man to man by the infected female sand flies. Children and young adults are most commonly affected[1-3]. In Bangladesh, 20 million people are considered to be at risk for Kala-azar[4]. Sodium stibogluconate (Sb^{v+}) is the first line drug in treatment of Kala-azar[1-3]. The optimum regimen of treatment with Sb^{v+} has not been established. WHO (1948) suggested that the optimal regimen of treatment with sodium stibogluconate should be established for each geographical region because regimen of treatment varies from one endemic area to another[5]. Manson Bahr originally

suggested 6 days treatment with 6ml Sb^{v+} daily for Indian Kala-azar[6] and 30 days treatment regimen for Kenyan Kala-azar patients[7]. Thakur et al showed that Manson Bahr's original regimen was grossly inadequate for these patients and suggested for longer course of treatment[8]. They recently

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suggested that Sb^{v+} at a dose of 20 mg/kg body weight/day should be given for at least 40 days[9]. The World Health Organization (WHO) recommended at a dose of 20mg/kg body weight/ day to a maximum 85 ml for minimum 20 days in Kala-azar patients[10]. In China 6 days course of Sb^{v+} was reported to result in a cure rate of over 90%[11]. So these data show clearly the variation in the regimen of Sb^{v+} for the treatment of Kala-azar in different countries.

There is a sharp increase in Kala-azar cases in various parts of Bangladesh[12-13]. No exclusive study has been done for paediatric Kala-azar patients with Sb^{v+}. We, therefore, undertook a randomized trial on four different regimens of treatment with sodium stibogluconate to find out which is the simplest and most effective treatment of Kala-azar in children of Bangladesh.

Patients and Methods

Eighty patients below 12 years of age with suspected Kala-azar were admitted in the paediatric ward of Rajshahi Medical College Hospital for the last 2 years. Study carried out retrospectively, detailed history and thorough physical examination were done. In all cases, body weight temperature chart and duration of illness were maintained. Splenic enlargement was measured in cm along its long axis from left costal margin in anterior axillary line. Liver enlargement was measured in cm from right costal margin in mid clavicular line. Hemoglobin estimation, erythrocyte sedimentation rate, total and differential white cell count were done in all cases. In selected cases platelet count, bleeding time, clotting time, blood urea, albumin and globulin ratio, chest radiography and electrocardiography (ECG) were done.

Bone marrow or splenic aspirates stained with Geimsa were examined for LD body. Aldelyde test was done in all cases but CFT or DAT tests were done in selected cases, but other serological tests like ELISA was not possible due to lack of facilities. Patients with strong clinical suspicion of Kala-azar having positive both Aldelyde test (AT) and complement fixation test (CFT), were also included in the study even if the bone marrow of splenic aspirate failed to reveal LD body. Patients were excluded if they had hemoglobin concentration below 30 gm/l, had complications such as tuberculosis, pneumonia, jaundice and renal or cardiac disease or had received anti-leishmenial treatment before coming to the hospital Twenty five (25) cases were thus left out from the study and five (5) cases absconded. Therefore, altogether 50 patients (27 male and 23 female) remained for analysis.

The patients were randomly allocated to four different regimens of stibogluconate (Sb^{v+}) intravenously (Stibatin 100 mg/ml). In group 'A' patients were given the drug for 20 days at a dosage of 10 mg/kg body weight daily. Patients in group 'B' received the drug for 20 days at a dosage of 15 mg/kg body weight daily for 20 days. Patients in group C received the drug at a dose of 10 mg/kg body weight twice daily for 20 days. Patients in group 'D' received the drug at a dosage of 20 mg/kg body weight daily for 40 days. During assessment of treatment patients were observed daily and spleen and liver measured weekly. Evidence of drug toxicity was sought by daily enquiry for any new symptom or any new sign. After the end of treatment in each group the patients were again clinically assessed and investigations were repeated. Remission of temperature, regression in the size of the liver and spleen, steady weight gain and improvement in haemoglobin level indicated initial cure.

Parasitological cure was indicated by the absence of parasite on bone marrow or splenic smear examination after treatment. Apparent cure was taken as initial cure and confirmed with parasitological cure. Relapse was indicated as the reappearance of parasite in the bone marrow or spleen and recurrence of clinical and laboratory abnormalities after initial cure. Ultimate cure was taken as clinical and parasitological cure with no relapse during 6 months follow up.

The patients were asked to attend for follow up after 1, 3 and 6 months of treatment or immediately if they developed fever or

enlargement of spleen. At each follow up, patients were examined clinically and routine investigations were done. Bone marrow or splenic aspirations were done at the final to follow up or when the patients showed the features of relapse. Relapse patients were treated with sodium stibogluconate (Sb^{v+}) at a dosage of 20 mg/kg body weight daily for 40 days.

Results

In four treatment groups to compare 50 children patients remained for analysis, Initial clinical findings in four regimens of treatment were shown in (Table-I). There were 13 patients each in A & C and 12 patients each in B and D groups.

The apparent cure rate of all four regimens of treatment was 100%.

Patients with minor side effects continued the drug with symptomatic treatment. Side effects were more in 40 days regimen than in 20 days regimen (Table-II). Headache with fever during treatment was the most common side effect. Some patients afebrile prior to treatment developed fever with the beginning of treatment. Epistaxis was the commonest bleeding manifestation that developed during treatment, sometimes the bleeding manifestations stopped with the stoppage of the drug and recurred with the resumption of the drug, the platelet count, BT, CT were normal in these patients before and during therapy. On the 37^{th} days of treatment in group D regimen, one patient developed sudden arrhythmia and ECG changes were suggestive of myocarditis and chest X-ray P/A view showed enlarged heart in transverse diameter, but changes reversed after the drug was stopped for 7 days. Then the drug was continued for next 3 days and the patient improved.

Only 27 (54%) patients could be followed up for 6 months. Two patients in group A and none from B, C and D groups relapsed (Table-III), Two relapsed cases were then treated with 20mg/kg body weight/day of sodium stibogluconate for 40 days. The responded with this regimen but could not be followed up further.

Discussion

In this study the regimen B, C and D were more effective with cure rates of 100% each as compared to the regimen A where the rate was 71.4%. Difference between regimen of A and B, C and D group were statistically significant at 95% confidence level. On the other hand the side effects were more common and more severe in regimen D compared to that in regimens A B & C. Severs side of effects, necessitating withdrawal of the drug occurred in regimen. D. The side effects in regimen A B and C were milder and the drug could be continued in all cases of these groups. These observations were different from those made on Indian and Kenyan Kala-azar patients[9-12]. Thakur et al in India showed that with 20mg/kg/day of Sb^{v+} increasing the duration of treatment increases cure rate without more toxicity. Chulay at al[17] also found that the drug was safe in higher dosage given for a longer duration in Kenyan patients. In this study, no case had primary unresponsiveness, which is not reflected in other studies[11, 14,18].

The relapse rate in group A was 15.3% and low from BCD groups. This finding was not similar to the other studies[9, 14, 20].

However, in this study, all the patients were cured by Sb^{v+} but the response to treatment varied from case to case. Such individual variation in response to Sb^{v+} therapy had also been found in other studies [6, 8, 11]. Which could identify two types of responders the fast responders and slow responders. The fast responders responded quickly and become afebrile within a week and their spleen regressed quickly. The slow responders took more than a week to respond and their spleen regressed slowly. This variation could be limited with individual variation in the metabolism of Sb^{v+}[19].

In this study, groups B, C and D regiments were almost same. In group D, one patient developed myocarditis and in group C Twice-daily dose was disadvantageous for the patients. Besides this, twice daily dose in group C and once daily dose in a group D the cumulative toxicity was more than group B.

Table I: Initial clinical findings four groups of patients with Kala-azar (n=50)

	Group-A	**Group**-B	**Group**-C	**Group**-D
No. of patients in the group	13	12	13	12
No. of male patients	7	6	7	7
No. of female patients	6	6	6	5
Mean (±SD) duration of illness (month)	4.2 (±2.6)	4.6(±2.4)	4.4(±2.6)	4.1(±1.5)
Mean (±SD) splenic size (cm)	6.1(±1.5)	7.1(±2.1)	7.2(±2.5)	7.1(±3.1))
Mean (±SD) WBC count ($X10^9$/L)	5.6(±2.9)	6.5(±3.5)	4.2(±2.0)	4.1(±4.7)
Mean Hb conc. (%)	45	50	45	45
No. of LD body positive patients	11	11	13	11
No. of LD body -ve but sero positive patients	2	1	0	1

Table II: Side effect and tolerance of regimens of treatment with stibofgluconate, (values are number of Patients)

Side effect	**Group-A**	**Group-B**	**Group-C**	**Group-D**	**Total**
	N-13	**n-12**	**n-13**	**n-12**	**n-50**
1. Allergic reaction	1	1	1	1	1
2, Headache with fever	2	1	1	3	2
3. Bleeding manifestations	1	0	0	2	3
4. Arthralgia	1	0	0	2	3
5. Pain & Swelling at the site of injection	1	0	0	0	1
6. Muscle pain	1	1	0	1	3
7. Vomiting	0	0	0	1	1
8. Abdominal pain	0	1	0	1	2
9. Cough	1	0	0	1	2
10. Fever with ECG changes	0	0	0	1	1

Table III: Ultimate rate of cure at six months follow up of four regimens of treatment with stibogluconate (Figures in parenthesis indicate percentage)

Regimen	**Total No.**	**No. Followed up**	**No. Relapsed**	**Ultimate Cure (%)**
A	13	7(53.8)	2(71.4)	5(71.4)
B	12	7(53.8)	7(100)	7(100)
C	13	7(53.8)	7(100)	7(100)
D	12	6(50.5)	6(100)	6(600)

A vs B was P<0.10 A vs C was P<0.10 and A vs D wasl P<0.10

Conclusion

Sodium stibogluconate in the dose of 15 mg/kg body weight (group B) once daily intravenously for 20 days had the best cure rate with least toxicity and may be recommended for routine treatment of childhood Kala-azar patients in Bangladesh.

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