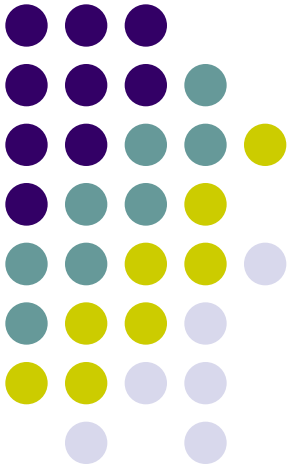
Effectiveness and Outcome of Single dose Liposomal Amphotericin B in Patients with Visceral Leishmaniasis



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Introduction

- Visceral leishmaniasis (VL), also called Kala-azar, is a vector borne neglected disease ranked by the WHO as the infectious disease with the ninth highest burden worldwide.
- More than 90% of the world's VL cases occur in three regions:

  1. Southern Asia, particularly Bihar State in northeastern India, Bangladesh and Nepal

  2. Eastern Africa (Sudan and neighboring countries)

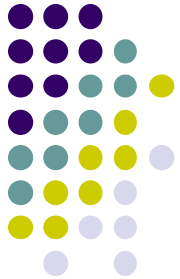
  3. The Americas, particularly northeastern Brazil.

Introduction(cont..)

- The predominant etiologic agents are L. donovani in southern Asia and eastern Africa, and L. infantum / L. chagasi elsewhere in the Old and New Worlds.

- The annual incidence for Bangladesh - between 12,400 and 24,900 cases. 45 districts and 105 subdistricts are affected.

Introduction(cont..)



- Within the last decade new drugs have been developed like paromomycin, miltefosine, and liposomal amphotericin B (LAmB), providing additional treatment options to sodium stibogluconate and amphotericin B deoxycholate.
- Recent studies in India show that a single intravenous infusion of liposomal amphotericin B (sLAmB) at 10 mg/kg is highly effective in India, which is a great improvement over the 28-day oral application of miltefosine or long term injections of paromomycin.

Introduction(cont..)

- A study in the five most VL endemic upazilas in Mymensingh district of Bangladesh noted that implementation of sLAmB was technically and operationally feasible.

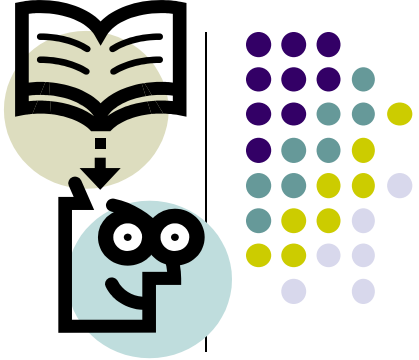
- WHO Regional Technical Advisory Group for Leishmaniasis suggested to use sLAmB as the first line drug for the VL elimination programme in the Indian subcontinent.

Introduction(cont..)

- As the efficacy and safety of sLAmB has been proven, the drug is established as First line agent in National guideline.

- The drug's effectiveness in national programme need to be scrutinized critically with observation of outcome. Hence the effectiveness and outcome of sLAmB in patients with VL in a tertiary care Hospital of Bangladesh was assessed.

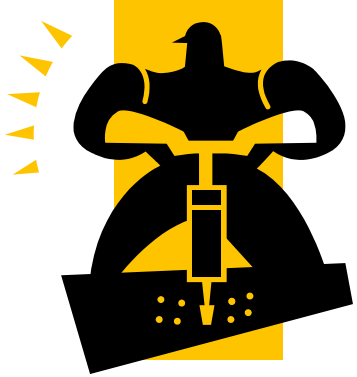
Rationale of the study



- This study aimed to assess the effectiveness and safety of a 10 mg/kg sLAmB regimen in VL a tertiary care hospital in Bangladesh.

- Results would not only serve the national VL control programme of Bangladesh, but will also ensure the drug’s effectiveness in individual case management and safety.

Methodology



- **Place of study :** Department of Medicine and Paediatrics, Dhaka Medical College Hospital.
- **Study period:** December 2015 to June 2016.

- **Study population:** All consecutive adult and paediatric patients who were admitted as diagnosed cases of VL or diagnosed as cases of VL after admission with Parasitological confirmation were enrolled for the study.

Inclusion criteria

- Patients between 2 and 65 years if they had symptoms and signs of leishmaniasis (e.g., fever more than two weeks, weight loss, anaemia and splenomegaly).
- rK39 rapid test positivity
- Parasites shown on microscopy of a splenic aspirate smear, liver biopsy or bone marrow.

Exclusion criteria

- Serious concurrent infection (TB or pneumonia).
- White-cell count -less than 750/cmm, Hb level < 3.5 g/dl & platelet count < 40000/ cmm.
- Hepatic and renal impairment
- Anti-leishmanial or unlicensed investigational treatments within six months.
- Pregnant women.

Study profile

34 diagnosed with VL by hospital doctors according to natoinal guidelines and offered study Rx

34 patients or guardians agreed to participate

1 has concomittant HIV infection
2 has previous H/O VL

31 Enrolled

1 did't receive study drug (As LAB was not available at that time)

30 Received complete treatment

30 Assessed for initial cure at day 30 and complete cure at day 180

29 fully treated

29 fully treated improved clinically, improving Resolution of fever and decrease in spleen size

1 didn't improve clinically (confirmed pathologically)

29 had final cure

RESULTS

Efficacy of single dose liposomal amphotericin B for visceral leishmaniasis (n=30)

	Intention-to-treat analysis		Per-protocol analysis	
By age group	**n/N (%)**	**Difference (95% CI; p value)**	**n/N (%)**	**Difference (95% CI; p value)**
Initial cure		8.5% (0.09-14.83; 0.613)		8.5% (0.09-14.83; 0.613)
Child	10/11 (90.9%)		10/11 (90.9%)	
Adult	17/19 (89.5%)		17/19 (89.5%)	
Final cure		0.0% (0.0-32.37; 0.77)		0.0% (0.0-32.37; 0.77)
Child	11/11 (100.0%)		11/11(100.0)	
Adult	18/19 (94.7%)		18/19(94.7%)	

Overall Efficacy	**29/30 (96.7%)**

Distribution of the patients by fever and appetite in different follow up (n=30)

Variables	Frequency	Percentage
Fever		
Before treatment	28	93.3
1st visit (after 1 month)	1	3.3
2nd visit (after 6 months)	1	3.3
Appetite improvement		
1st visit (after 1 month)	29	96.7
2nd visit (after 6 months)	29	96.7

Comparison of clinical and lab parameters before and after anti-leishmaniasis treatment (n=30)

Parameters	Before treatment	1st visit (1 month)	2nd visit (6 months)
Hb (gm/dl)	9.6 ± 5.1	10.56 ± 0.96	11.26 ± 0.98
Weight (kg)	38.82 ± 12.54	41.89 ± 12.30	44.93 ± 12.03
Spleen size (cm below left costal margin)	6.5 ± 3.3	2.78 ± 2.55	0.53 ± 1.30
Statistical analysis	**P value**		
Before treatment vs 1st visit	< 0.001*		
Before treatment vs 2nd visit	<0.001*		

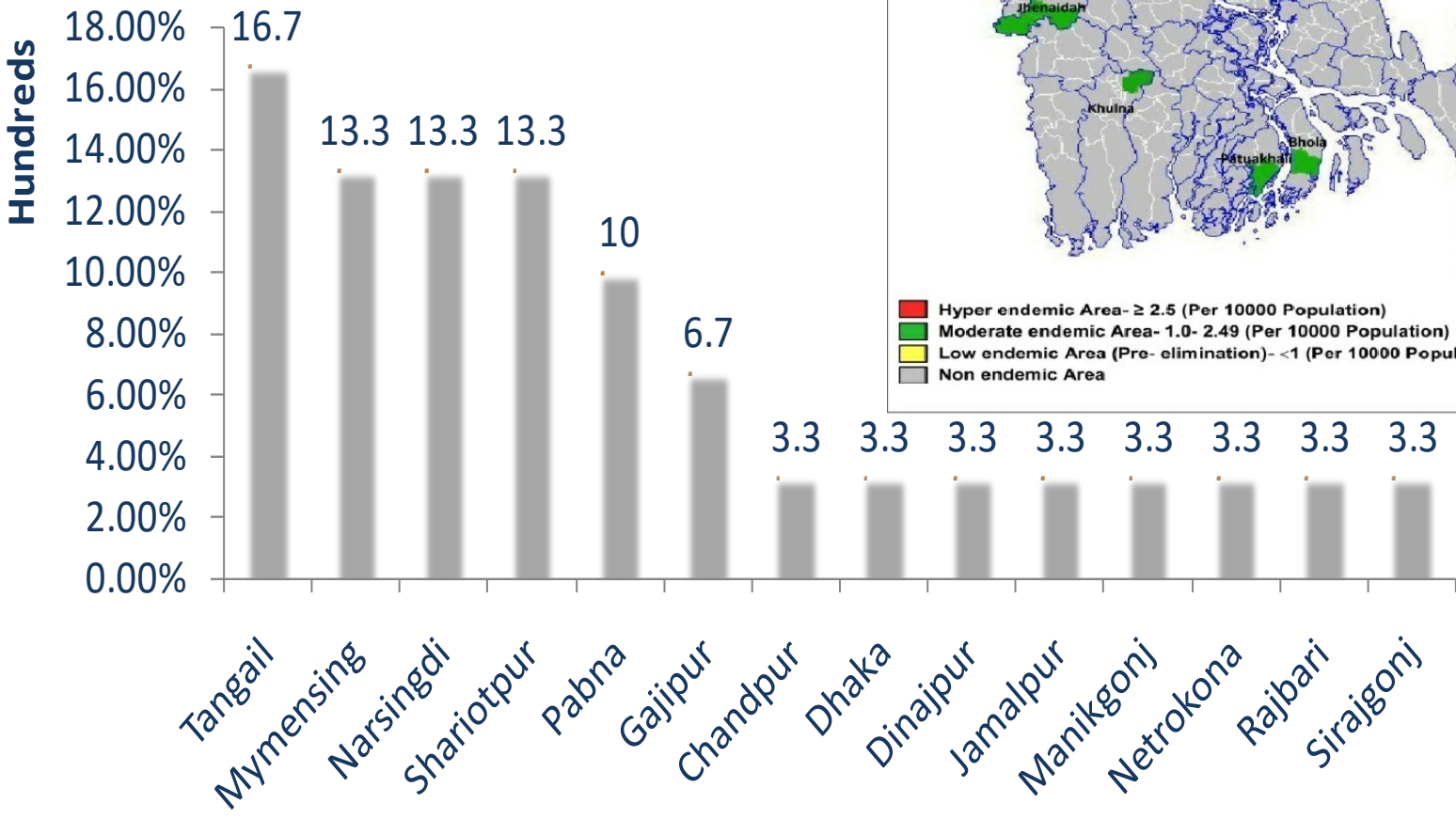
Distribution of the study patients by baseline characteristics (n=30)

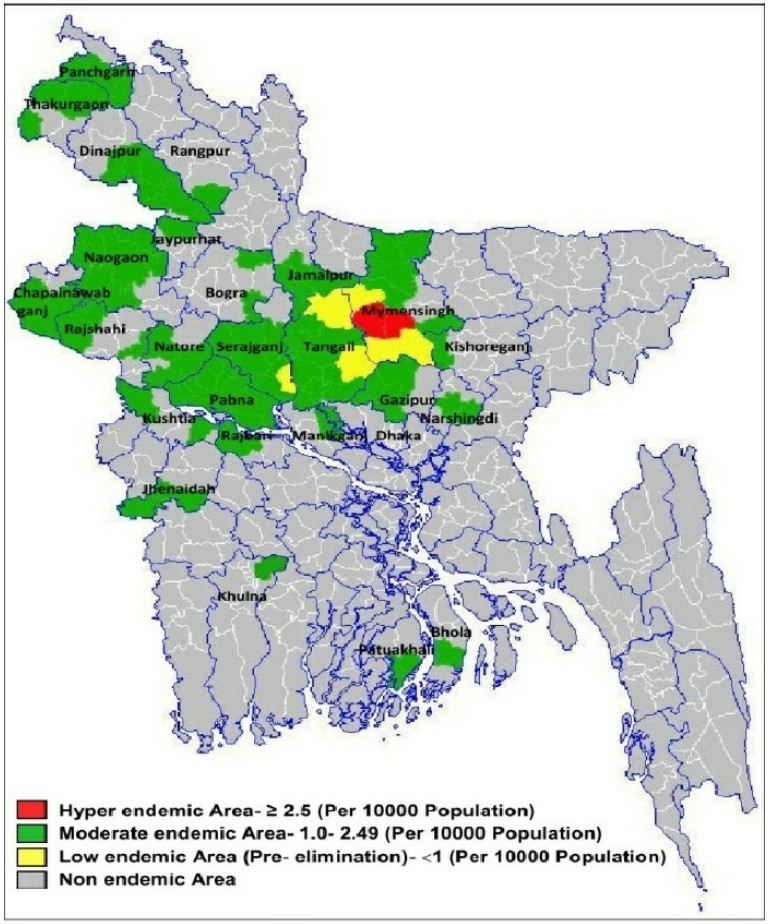
Baseline characteristics	Children (< 18 yrs) (n=11)	Adults (≥ 18 yrs) (n=19)	Overall (n=30)
Age (years)			
Mean ± SD	11.4 ± 3.4	33.2 ± 11.4	21 ± 13.42
Median (IQR)	10 (8 - 13)	31 (23 - 44)	14 (8-28)
Sex			
Male	6 (54.5%)	12 (63.2%)	18 (60.0%)
Female	5 (45.5%)	7 (36.8%)	12 (40.0%)
BMI (kg/m^2)			
Mean ± SD	13.8 ± 1.8	17.5 ± 2.3	16.3 ± 2.6
Underweight	8 (72.7%)	14 (73.7%)	22 (73.3%)
Pulse (beat/min)	97.4 (66 - 128)	85.5 (60 - 120)	92.4 (60 - 128)

Distribution of the study patients according to house type (n=30)

House type	Frequency	Percentage (%)
Kacha ghar	18	60.0
Tinshed	9	30.0
Building	3	10.0

Ditribution of patients according to residence (n=30)





Clinical features in kala-azar patients (n=30)

Physical Sign	Number of patient	Percentage
Fever	28	93.3
Anaemia	28	93.3
Jaundice	5	16.7
Lymphadenopathy	1	3.3

Splenomegaly (n=30)

Spleen size at enrollment (cm)	Children (< 18 yrs) (n=11)	Adults (≥ 18 yrs) (n=19)	Overall (n=30)
Mean ± SD	6.8 ± 3.4	6.3 ± 3.2	6.5 ± 3.3
≤ 5 cm	5 (45.5%)	3 (15.8%)	8 (26.7%)
5 - <10 cm	4 (36.4%)	9 (47.4%)	13 (43.3%)
≥ 10 cm	2 (18.2%)	6 (31.6%)	8 (26.7%)
Not palpable	0	1(5.3%)	1 (3.3%)

Hepatomegaly (n=30)

Hepatic enlargement (cm)	Number of patient	Percentage
<4 cm	9	30.0
4 - 8 cm	10	33.3
> 8 cm	5	16.7
Not palpable	6	20.0
Total	30	100.0

Demonstration of LD body (n=30)

Materials	Number of positive patient	Percentage
Bone marrow aspiration	15	50.0
Splenic aspiration	14	46.7
Liver biopsy	1	3.3

Distribution of the study patients by adverse effects (n=30)

Adverse effects	Number of positive patient	Percentage
Fever	7	23.3
Shivering	5	16.7
Renal impairment	1	3.3
Back pain	1	3.3

Discussion

- In the current study, cure rate was 96.7%. When statistically calculated by intention-to-treat and per-protocol analysis results 100% effective in children and 94.7% in adult population.

- Lucero et al. demonstrated cure rates at 6 and 12 months were 98.7% and 96.4%, respectively. In Nepal after 12 months final cure rate was 79%.

Discussion (cont…)

- In present study, marked improvement of Hb (g/dl) level occurred after treatment with sLAmB.

- Before treatment mean Hb was 9.6 ± 5.1, after 1 month Hb level significantly increased to 10.56 ± 0.96 and after 6 months 11.26 ± 0.98.

Discussion (Cont…)

- In our study, mean weight was significantly raised from baseline (38.82 ± 12.54 kg) to after 1 month (41.89 ± 12.30kg) and 6 months (44.93 ± 12.03) after treatment with sLAmB.

Discussion (cont…)

- In this study, there was marked reduction of spleen size of VL patients after treatment with sLAmB.
- Before treatment mean spleen was 6.5 ± 3.3 cm, after 1 month of treatment spleen reduced significantly to 2.78 ± 2.55 cm and after 6 months it was 0.53 ± 1.30 cm.

Discussion (cont…)

- In the present series, no referral was necessary because all adverse events were mild. Incidence of adverse events was about 43.3%.

- Among them 23.3% patients had fever, shivering present in 16.7% cases and renal impairment in 3.3%.

Conclusion

- 10 mg/kg single dose liposomal amphotericin B is a safe and effective treatment for primary VL in Bangladesh.

- A follow-up period of 6 months is required to capture the majority of VL relapse cases and VL relapse is predicted by low Hb and large spleen size and failure to weight gain at the end of treatment.


thank you!