Efficacy and safety of pharmacotherapeutic interventions used in visceral leishmaniasis: A systematic review and network meta-analysis of randomized clinical trials

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Background and Aim

Visceral leishmaniasis (VL) or **kala-azar**, caused by **parasite Leishmania (L.) donovani**, is seen as a neglected endemic in Asia, East and North Africa, South America, and Southern Europe. **Several drugs have been tested** in visceral leishmaniasis (VL) globally; however, evidence-based results comparing their safe and effective use are **not available** for use in clinical practice. Hence, this study aimed to provide a **comparative analysis of efficacy and safety outcomes** with different antileishmanial agents used in VL.

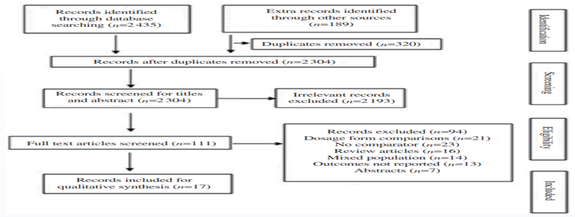
Methodology

The current review was performed and reported in accordance with the preferred reporting items for systematic reviews and network meta-analyses (**PRISMA-NMA**). A systematic literature search in PubMed/Medline, EMBASE, Cochrane, and Google Scholar was done using keywords - "randomized controlled trials (**RCTs**)", "**antileishmanial**" and "**visceral leishmaniasis**". The **outcomes** included were **cure rate**, **overall withdrawals, relapse rate**, and treatment- emergent adverse events (**TEAEs**). Effect estimates through frequentist NMA approach were presented as odds ratio (**OR**) with 95% confidence interval (CI). **Rankogram** plots were used for identifying the 'best intervention' based on **p- scores** obtained using the surface under the cumulative ranking (**SUCRA**). The risk of bias was evaluated by using Pedro Scale.

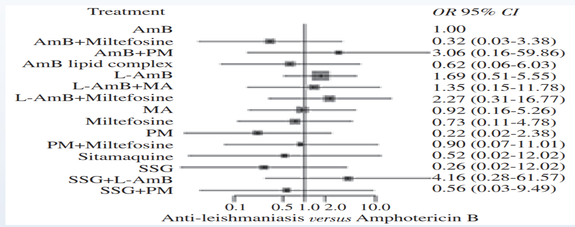
Results

Seventeen RCTs with **5,143** VL patients who received **different antileishmanal agents** *Amphotericin B, Miltefosine, Paromomycin (PM), Meglumine antimoniate (MA), Sodium stibogluconate (SSG), Sitamaquine, Pentavalent antimonials (PA)+, met the **inclusion criteria** and were included. For efficacy outcome, cure rate, the NMA rankogram analysis revealed that **PM *p-score= 0.8148+** had a **highest probability** of being **best** in the pool, followed by **SSG** *OR: 0.82; CI: 0.24-2.79, p-score=0.7580+, **AmB + Miltefosine** *OR: 0.66; CI: 0.02-19.04, p-score= 0.7329+ as compared to remaining treatments; however, the most of the **TEAEs** were reported with **Sitamaquine.** Meanwhile the differences were **statistically non-significant**.

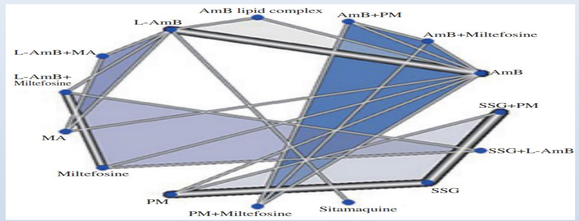
PRISMA Flow diagram (Study Selection Process)



Pair-wise meta-analysis in NMA for cure rate



Network plot of interventions reporting cure rate as outcome

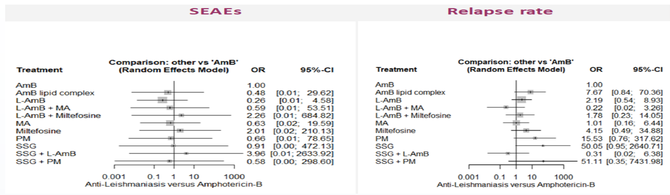


Ranking probabilities of interventions reporting cure rate

Rank	Intervention	P-score
1	PM	0.8148
2	SSG	0.7580
3	AmB+Miltefosine	0.7329
4	Sitamaquine	0.6115
5	AmB lipid complex	0.5879
6	Miltefosine	0.5707
7	SSG+PM	0.5645
8	MA	0.5002
9	PM+Miltefosine	0.4953
10	AmB	0.4707
11	L-AmB+MA	0.3965
12	L-AmB	0.3076
13	L-AmB+Miltefosine	0.2643
14	AmB+PM	0.2478
15	SSG+L-AmB	0.1772

Abbreviations; Amphotericin B (AmB), Miltefosine, Liposomal amphotericin B (L-AmB), Paromomycin (PM), Meglumine antimoniate (MA), Sodium stiboglconate (SSG), Sitamaquine, Pentavalent antimonials (PA)

Pair-wise meta analysis in NMA



Network Plot

Ranking Probabilities

Intervention	P-score	Rank
L-AmB	0.6953	1
AmB lipid complex	0.5756	2
SSG+PM	0.5511	3
L-AmB+MA	0.5438	4
MA	0.5374	5
PM	0.5345	6
SSG	0.4832	7
AmB	0.4585	8
Miltefosine	0.3957	9
L-AmB+Miltefosine	0.3931	10
SSG+L-AmB	0.3317	11

Intervention	P-score	Rank
L-AmB+MA	0.9104	1
SSG+L-AmB	0.8644	2
AmB	0.7182	3
MA	0.7008	4
L-AmB+Miltefosine	0.5805	5
L-AmB	0.5131	6
Miltefosine	0.3752	7
AmB lipid complex	0.2910	8
PM	0.2540	9
SSG+PM	0.1637	10
SSG	0.1288	11

PEDro Checklist

Authors, year	Total score
Seaman, 1993	7
Jha, 1998	7
Thakur, 2000	7
Sundar, 2002	7
Sundar, 2004	7
Sundar, 2007	7
Sundar, 2008	7
Sundar, 2010	7
Hailu, 2010	7
Sundar, 2011	7
Musa, 2012	7
Sundar, 2014	7
Wasunna, 2016	7
Rahman, 2017	7
Romero, 2017	7
Borges, 2017	7
Goswami, 2020	7

Conclusion

·The present study has evaluated the multiple available treatment options recommended in visceral leishmaniasis management and provided the effect size estimates despite the absence of head-to-head clinical studies.

·Paromomycin reported the advantage in comparison to other agents in achieving higher cure rates.

·L-AmB plus MA combination was associated with high relapse rates while L-AmB alone reported the maximum SEAs.

·Future research with direct head-to-head RCTs and timely update of new findings is warranted to further strengthen these results.

References

1. Wamai RG, Kahn J, McGloin J, Ziaggi G. Visceral leishmaniasis: A global overview. J Glob Health Sci 2020; 14: 2(1).

2. Mann S, Frasca K, Scherrer S, Henao-Martínez AF, Newman S, Ramanan P, et al. A review of leishmaniasis: Current knowledge and future directions. Curr Trop Med Rep 2021; 8(2): 121-132.

3. Sundar S, Mehta H, Suresh AV, Singh SP, Madhukar R, Murray HW. Amphotericin B treatment for Indian visceral leishmaniasis: Conventional versus lipid formulations. Clin Infect Dis 2004; 38(3): 377- 383.

4. Pokharel P, Ghimire R, Lamichhane P. Efficacy and safety of paromomycin for visceral leishmaniasis: A systematic review. J Trop Med 2021; 2021: 8629039.