International Journal of Research in Medical Sciences
Premachandran AM et al. Int J Res Med Sci. 2023 Apr;11(4):1246-1250
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20230869

Original Research Article

Amphotericin B in the management of COVID-19 associated mucormycosis

Architha M. Premachandran[1], Pruthvi R. Shivalingaiah[1], Ashwini Godse[2], Arunima Sheeja[1]*, Ravishankar Chandrashekar[2]

[1]Department of Otorhinolaryngology, Shri Atal Bihari Vajpayee Medical College and Research Institute, Bangalore, Karnataka, India
[2]Department of Otorhinolaryngology, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India

Received: 02 February 2023
Revised: 03 March 2023
Accepted: 06 March 2023

***Correspondence:**
Dr. Arunima Sheeja,
E-mail: drarunima2793@gmail.com

ABSTRACT

Background: Amphotericin B is considered the drug of choice for primary treatment of mucormycosis. During second wave of COVID-19 pandemic there was severe scarcity of liposomal amphotericin B. This study aims to determine role of various formulations of amphotericin and their side effects when used for the treatment of COVID-19 associated mucormycosis.
Methods: A retrospective study was conducted between May 2021 and December 2021 at a tertiary care centre. 380 patients with post-COVID rhino-orbito-cerebral mucromycosis (ROCM) were included in the study. Liposomal amphotericin B, conventional amphotericin deoxycholate, lipid complex amphotericin B was used in the treatment. Patients were observed for side effects like fever, chills, rigors, hypokalemia, renal function derangements, thrombophlebitis and respiratory difficulties.
Results: Majority of patients received liposomal amphotericin B (331) and 31 patients received conventional amphotericin deoxycholate and 5 patients were given lipid complex amphotericin B injections. The most commonly encountered side effects were of the mild type constituting chills (98% with liposomal and 100% with amphotericin deoxycholate), and fever (94% with liposomal and 74% with amphotericin deoxycholate).
Conclusions: Our study highlights the role of various formulations of amphotericin B in the treatment of COVID-19 mucormycosis.

Keywords: Amphotericin deoxycholate, Liposomal amphotericin B, COVID associated mucormycosis

INTRODUCTION

Mucormycosis is a spectrum of chronic, subacute and rapidly progressing infections caused by fungi of the mucorale order of the class zygomycetes. It mainly affects immunocompromised patients with severe underlying diseases such as uncontrolled diabetes mellitus, hematologic malignancies, and organ transplant patients.[1]

Management of mucormycosis involves a multidisciplinary approach. Principles of treatment include early clinical and laboratory diagnosis, initiation of antifungal therapy, surgical debridement of necrotic lesions, control of underlying medical condition.[2]

Amphotericin B is considered the drug of choice for primary treatment of mucormycosis. It is a polyene antimicrobial that acts by binding to sterols in the fungal cell membrane and causes a change in membrane permeability. Lipid formulations of amphotericin B, and liposomal amphotericin have better therapeutic index than conventional amphotericin B. Standard daily dose of

liposomal amphotericin B is 5 mg-10 mg/kg/day and conventional amphotericin in 1 mg-1.5 mg/kg/day. Liposomal amphotericin is less toxic than conventional amphotericin B.[3]

Prompt and aggressive intervention is an essential part of treatment of mucormycosis due to the rapid progression of the disease.[4-6] Survival rate is found to be around 80 % with the introduction of combined therapy with amphotericin B and surgery.[5-7]

The initial formulation was amphotericin B deoxycholate (DAmB), which was developed in the 1950s. For many decades DAmB was the only antifungal agent available for the treatment of invasive fungal diseases. However, the significant dose-limiting toxicity of DAmB (most notably nephrotoxicity and infusion-related reactions) provided the impetus to develop new less toxic formulations. Liposomal amphotericin B is a unique lipid formulation of amphotericin B that has been used for nearly 20 years to treat a broad range of fungal infections. While the antifungal activity of amphotericin B is retained following its incorporation into a liposome bilayer, its toxicity is significantly reduced.[10]

This lipid-based formulation increases the circulation time and alters the biodistribution of the associated amphotericin B. Drugs complexed with lipid vehicles have a longer residence time in the vasculature, hence, they are able to localize and reach greater concentrations in tissues with increased capillary permeability (i.e., infection and inflammation) compared with regions of normal tissue, which are essentially impermeable to lipid–complex drugs. This method of increasing the localization of drugs to diseased sites is referred to as passive targeting.[9,11,12]

During second wave of COVID-19 pandemic there was severe scarcity of liposomal amphotericin B in the initial surge of rhino-orbito cerebral mucormycosis (ROCM) cases. Hence we had to use various available formulations (conventional amphotericin, liposomal, lipid complex). This study aims to determine role of various formulations of amphotericin and their side effects when used for the treatment of COVID-19 associated mucormycosis.

METHODS

A retrospective descriptive (record based) study was conducted between May 2021 and December 2021 at Bowring and Lady Curzon hospital, Shri Atal Bihari Vajpayee Medical College and Research Institute, Karnataka, India. 380 patients with post-COVID ROCM were included in the study. Post-COVID reverse transcriptase polymerase chain reaction (RTPCR) negative ROCM who were histopathologically and/or radiologically proven mucormycosis [European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG group) criteria].[8] Patients with no history of RTPCR positive COVID 19 infection and RTPCR positive ROCM were excluded.

Patients fulfilling the inclusion criteria were enrolled for the study after obtaining approval and clearance from institutional ethics committee. Patient's demographic details, clinical features, clinical procedures, laboratory test results, radiological reports and details of medical and surgical interventions performed was collected using a detailed proforma from the medical records. Patients admitted were evaluated preoperatively with diagnostic nasal endoscopy. Preoperative magnetic resonance imaging (MRI) was done on the patients to determine the extent of the disease. Preoperative investigations, ophthalmologic and oral maxillofacial surgery evaluation is done on the patients. Patients underwent surgical debridement after the evaluation.

Liposomal amphotericin B (5-10 mg/kg/day) and/or conventional amphotericin (1-1.5 mg/kg/day) was given to the included patients preoperatively and after endoscopic debridement for three weeks. Daily renal function test (RFT), serum electrolytes and blood sugars were monitored. Patients were observed for side effects like fever, chills, rigors, hypokalemia, renal function derangements, thrombophlebitis and respiratory difficulties. Data collected in the proforma was collated in Microsoft excel and analysed statistically using statistical package for the social sciences (SPSS) software version 24.

RESULTS

In our study, among the patients affected with mucormycosis, 262 were male and 118 were females (Table 1). Different formulations of amphotericin injections were used based on the availability. Majority of patients received liposomal amphotericin B (331) and 31 patients received conventional amphotericin B, 13 of them received both conventional and liposomal type of amphotericin B injections. Only 5 patients were given lipid complex amphotericin B injections (Figure 1). The various side effects observed were categorised into mild, moderate and severe based on the symptamatology.

Table 1: Demographic profile of patients.

Variables	Number
Total number of patients	380
Age group (years)	12-78
Median age (years)	45
Sex	
Male	262
Female	118

Around 15% of the patients developed breathing difficulty and 1.2% had bronchospasm following administration of liposomal amphotericin B which was in stark contrast with that of conventional amphotericin deoxycholate wherein

around 35% had breathing difficulty and 6.4% had bronchospasm. Even though lipid complex was administered only to 5 patients, 2 of them had breathing difficulty and 1 developed severe bronchospasm with severe desaturation of upto 45%. It was managed with oxygen administration, injection hydrocortisone and avil and nebulisation with budesonide. The side effects observed with various formulations of amphotericin B are represented in Table 2.

Table 2: Adverse effects of various formulations of amphotericin B.

Side effects	Liposomal (n=331)	Conventional (n=31)	Lipid complex (n=5)	% Liposomal	% Conventional	% Lipid complex
Mild						
Fever	314	23	5	0.948640483	0.741935484	1
Chills	327	31	5	0.987915408	1	1
Nausea and vomiting	293	30	5	0.885196375	0.967741935	1
Thrombophlebitis	132			0.398791541	0	0
	293	84	15	0.885196375	2.709677419	3
Moderate						
Breathing difficulty	51	11	2	0.15407855	0.35483871	0.4
Brochospasm	4	2	1	0.012084592	0.064516129	0.2
Chest pain	48	5		0.145015106	0.161290323	0
	103	18	3			
Severe						
Deranged renal function test (RFT)						
Serum creatinine	4	15		0.012084592	0.483870968	0
Serum urea	5	17		0.01510574	0.548387097	0
	9	32				
Electrolyte imbalance						
Hyponatremia	111	12	2	0.335347432	0.387096774	0.4
Hypokalemia	98	14	2	0.296072508	0.451612903	0.4
Hypomagnesemia	22	5		0.066465257	0.161290323	0

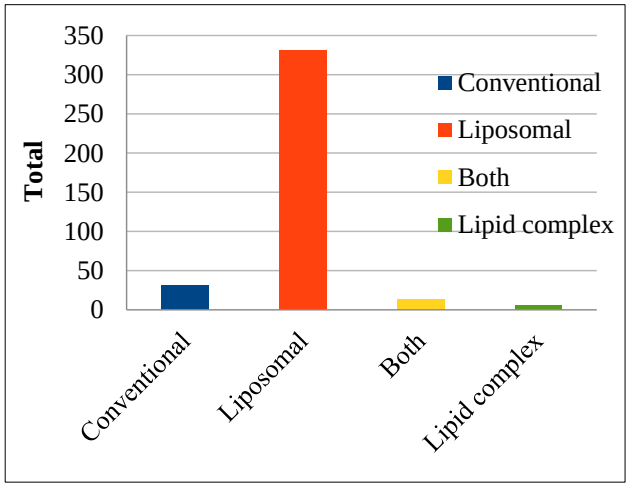

Figure 1: Different formulations of amphotericin received by patients.

DISCUSSION

Amphotericin B is the antifungal agent of choice. It is a polyene antimicrobial that acts by binding to the fungal cell membrane ergosterol, producing an aggregate that creates a transmembrane channel, allowing the cytoplasmic contents to leak out, leading to cell death. Successful treatment of mucormycosis requires surgical debridement of infected tissue, prompt institution of effective antifungal treatment, and correction of the underlying metabolic and immune derangement. The use of amphotericin B is often limited by frequent side effects. Complexing amphotericin B with lipid structures avoids most of the negative side effects, most importantly the dose-limiting nephrotoxicity. The principal acute toxicity of AmB deoxycholate includes nausea, vomiting, rigors, fever, hypertension or hypotension, and hypoxia.

In a phase 1 – II study made by Waish et al on the safety, tolerance and plasma pharmacokinetics of liposomal amphotericin in patients infected due to aspergillus and other filamentous fungi, maximal tolerated dosage was determined. It was found that maximal tolerated dosage was 15 mg/kg/day. Infusion related reactions of fever occurred in 19% and chills or rigors occurred in 12% of 43 patients. The study concluded that L-AMB at dosages as high as 15 mg/kg/day follows nonlinear saturation kinetics, is well tolerated and can provide effective therapy for aspergillosis and other filamentous fungal infections.[9]

In our study, the most commonly encountered side effects were of the mild type constituting chills (98% with liposomal and 100% with amphotericin deoxycholate), fever (94% with liposomal and 74% with amphotericin

deoxycholate). All patients who received Lipid complex formulations had developed fever and chills. Symptomatic treatment with injection paracetamol and injection avil was given for these patients. The administration of liposomal amphotericin B formulations led to the development of thrombophlebitis (39%) which was not seen in patients who received deoxycholate or lipid complex formulations. Topical application of thrombophob ointment containing benzyl nicotinate and heparin sodium and oral anti-inflammatory medications were given for the same.

Its principal chronic adverse effect is nephrotoxicity. Clinical manifestations of AmB nephrotoxicity include renal insufficiency, hypokalemia, hypomagnesemia, metabolic academia, and polyuria due to nephrogenic diabetes insipidus.

Passive targeting of liposomal formulations enhances delivery of the agent to the fungi, infected organs, and phagocytes with lower toxicity, while maintaining antifungal efficacy through significantly higher sustained tissue levels of the drug. Within these sites, drug release occurs through the action of lipases from surrounding inflammatory cells.[9,11,12]

The occurrence of nephrotoxicity with deranged serum urea and creatinine were more with conventional amphotericin deoxycholate (54% and 48% respectively) in comparison to liposomal amphotericin B (1.5% and 1.2% respectively). Conventional amphotericin deoxycholate showed more incidence of hypokalemia (45%) and hyponatremia (33%) in contrast to the liposomal amphotericin B. All cases had reversible type of nephrotoxicity which was achieved with correction of electrolytes with Potassium chloride injections and oral sodamint tablets based on the electrolyte levels. The incorporation of adequate drug holidays (2-3 days) in between the treatment had helped to decrease the development of fatal complications associated with side effects of the drug.

Liposomal amphotericin B is the drug of choice for treatment of mucormycosis. Even though conventional amphotericin B had higher incidence of side effects compared to liposomal amphotericin in our study, the side effects were mild and reversible. Hence, we were able to give conventional amphotericin to 31 patients when the availability of liposomal amphotericin was scarce initially due to large number of cases. Only 1 patient developed severe alteration in renal parameters (serum creatinine and urea) where we had to switch over to liposomal amphotericin. The overall survival and disease outcome was found to be good in both category formulations along with surgical debridement.

Limitations

The total number patients who received liposomal amphotericin were considerably higher in number in comparison to the conventional Amphotericin deoxycholate group due to its limited availability. Hence, statistical analysis could not be carried out satisfactorily.

CONCLUSION

Liposomal amphotericin B is the drug of choice for the management of COVID associated mucormycosis (CAM). It is associated with lesser side effects than conventional amphotericin B and lipid complex amphotericin B. Our study also highlights the fact that conventional amphotericin B can also be used during non-availability of liposomal formulations as it has proved its efficacy with adequate drug holidays to minimise the side effects.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Premachandran AM, Shivalingaiah PR, Godse A, Sheeja A, Chandrashekar R. Amphotericin B in the management of COVID-19 associated mucormycosis. Int J Res Med Sci 2023;11:1246-50.