European Journal of Molecular &Clinical Medicine

ISSN2515-8260 Volume 09, Issue 06,2022

Original Research Article

A comparative study of systemic antimycotic drug conventional and liposomal Amphotericin B in mucormycosis and its effects in post COVID patients

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Abstract

Mucormycosis is a fungal infection primarily affecting immunocompromised individuals. We have observed sudden rise of mucormycosis cases in post COVID 19 patients. Here we have reported 600 cases of mucormycosis associated with COVID 19.Liposomal amphotericin B was compared with conventional amphotericin B for antifungal therapy in mucormycosis, double-blind, multicentre trial.The two drugs were equivalent in overall efficacy. However, the liposomal amphotericin B treatment group had fewer proven fungal infections, fewer infusion-related side effects and less nephrotoxicity. Patient data from that study were analysed to compare the pharmacoeconomics of liposomal versus conventional amphotericin B therapy.Data from 600 patients were collected and analysed. Hospital costs from first dose were significantly higher for all patients who received liposomal amphotericin B. The mean duration of therapy was 10.8 days for liposomal amphotericin B (300 patients) and 10.3 days for conventional amphotericin B (300 patients). The composite rates of successful treatment were similar (50 percent for liposomal amphotericin B and 49 percent for conventional amphotericin B. The outcomes were similar with liposomal amphotericin B and conventional amphotericin B with respect to survival (93 percent and 90 percent, respectively. With the liposomal preparation significantly, fewer patients had infusion-related fever (17 percent vs. 46 percent), chills or rigors (18 percent vs. 55 percent), and other reactions, including hypotension, hypertension, and hypoxia. Nephrotoxic effects (defined by a serum creatinine level two times the upper limit of normal) were significantly less frequent among patients treated with liposomal amphotericin B (18 percent) than among those treated with conventional amphotericin B (37 percent, $p<0.001$).

Keywords: Conventional amphoterin B, liposomal amphoterin B, mucormycosis, COVID 19

Introduction

Mucormycosis or Zygomycosis also called Phycomycosis is an aggressive, rapidly progressive and life-threatening fungal infection. A hallmark of mucormycosis infection is the presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis[1]. Imaging techniques are not typically diagnostic.Only histological examination obtains a definitive diagnosis. Depending on the site of infection and underlying predisposing factors, mortality

ISSN2515-8260 Volume 09, Issue 06,2022

rates may vary from 20 to 100%. Early diagnosis and immediate intervention are crucial for such patients. Treatment includes control of the underlying disease, surgical debridement and systemic antifungal therapy. We have observed the sudden rise of mucormycosis cases in COVID-19 era.Here we have reported 600 cases of mucormycosis in post Covid-19 patients and compare conventional and liposomal amphotericin in mucormycosis and its effects.

Amphotericin B is a polyene antifungal agent with activity in vitro against a wide variety of fungal pathogens [2]. Amphotericin B exerts its antifungal effect by disruption of fungal cell wall synthesis because of its ability to bind to sterols, primarily ergosterol, which leads to the formation of pores that allow leakage of cellular components. This affinity may also account for its toxic effects against select mammalian cells.

Despite the advent of newer antifungal agents, Amphotericin B deoxycholate has been the 'gold standard' treatment for invasive fungal infections for over 40 years. Driven to improve on the renal toxicity of amphotericin B deoxycholate, pharmaceutical research has led to the development of several new antifungals including lipid formulations of amphotericin B, broad-spectrum azoles and echinocandins. Compared with amphotericin B deoxycholate, the lipid formulations of amphotericin B (amphotericin B lipid complex, amphotericin B colloidal dispersion and liposomal amphotericin B) share distinct advantages in improved drug safety, in particular reduced incidence and severity of amphotericin B deoxycholate-related nephrotoxicity. Although all these formulations contain AMB, they differ with regard to their lipid composition, shape, size, stability, pharmacokinetics and toxicity. However, the lipid formulations of amphotericin B are significantly more expensive than amphotericin B deoxycholate and, as for many of these new antifungals, there are as yet insufficient published studies to guide clinicians. This paper examines aspects of safety, efficacy, and health economic data for the liposomal amphotericin B in particular, in order to provide a rationale to justify substituting amphotericin B deoxycholate with the lipid formulations of amphotericin B. We compared liposomal amphotericin B and conventional amphotericin B in mucormycosis and its effect in post covid patients.

Material and Methods

This was a comparative cross-sectional study of 600 patients with duration of 10 months. All the patients with rhino orbital mucormycosis admitted under ENT department of civil hospital, Ahmedabad during from January to October 2021 were included in the study.In which 300 patients received conventional amphotericin b and 300 patients received liposomal amphotericin B. Demographic data such as age, sex etc. were noted. Patients' chief complaints were noted and thorough clinical examination was done. Sample collected from diseased tissue was sent for KOH and histopathological examination. Patients were advised necessary radiological investigation to know the anatomical variation and extent of the disease. Amphotericin B was started as soon as presence of mucormycosis was confirmed.

Administration of study drugs

Patients were conveniently sampled in a 1:1 ratio according to center to be treated initially with liposomal amphotericin B (3-5 mg per kilogram of body weight per day) or conventional amphotericin B (0.6-1 mg per kilogram per day). In order to take into account clinical practice patterns, adjustment of the dose of the study drug was permitted when there was evidence of infection or toxicity. When toxic effects occurred, reduction of the dose to 1.5 mg of liposomal amphotericin B per kilogram or 0.3 mg of conventional amphotericin B per kilogram was permitted.

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Monitoring of infusion-related toxicity

All infusion-related reactions were monitored prospectively. Before the first infusion, no premedications for the prevention of infusion-related reactions were permitted. If a patient had an infusion-related toxic reaction during the first infusion, it was treated.
Surgical debridement was planned after general anaesthesia checkup. Patients were evaluated post operatively by weekly nasal endoscopy with repeat biopsy.

Results

A total of 600 patients were enrolled in the study between January 2021 and October 2021. 300 patients received liposomal amphotericin B and 300 received conventional amphotericin B. Groups were balanced with respect to age, sex and risk category (Table 1)
We found that most common age group was 51-60 years of age as shown in Table 1. Out of total patients, 370 were males and 230 were females (n = 600). It showed male to female ratio of 1.60/1. Mean age was 56 years.
Diabetes Mellitus type II was found to be the most common etiological factor associated with mucormycosis as shown in Table 2. 80% patients had Diabetes Mellitus type II. Hypertension, ischemic heart disease and chronic kidney disease was reported in 35%, 7% and 6% patients respectively.KOH culture of representative tissue revealed presence of fungi in 86% patients, while biopsy suggestive of mucormycosis was reported in all 100 (100%) patients.

Dosage

The mean daily doses throughout the study were 3.0±0.9 mg per kilogram for liposomal amphotericin B and 0.6±0.2 mg per kilogram for conventional amphotericin B. The mean duration of therapy was similar for liposomal amphotericin B (10.8±8.9 days) and conventional amphotericin B (10.3±8.9 days).
There were also more dose reductions due to toxicity (both infusion-related and non-infusion-related adverse events) among patients treated with conventional amphotericin B (101 patients [33 percent]) than among those treated with liposomal amphotericin B (36 patients [12 percent], $p<0.001$).

Efficacy

The overall success rate according to the composite score was 47.3 percent for patients receiving liposomal amphotericin B and 46.6 percent for those receiving conventional amphotericin B (Table 2).
There was a trend toward improved survival among patients receiving liposomal amphotericin B; 25 patients receiving liposomal amphotericin B died, as compared with 36 receiving conventional amphotericin B (P=0.18).

Safety and Tolerance

Infusion-Related toxicity

A total of 6000 infusions were prospectively monitored: 3147 infusions in patients receiving liposomal amphotericin B and 2853 in those receiving conventional amphotericin B. Patients receiving liposomal amphotericin B had fewer infusion-related reactions than did those receiving conventional amphotericin B. This result was found for all infusions and also for the first infusion, when no premedication was permitted for prevention of infusion-related

toxicity (Table 4).

When all infusions were analyzed for infusion related reactions, infusion-related increases in temperature of more than 1°C occurred after 267 infusions of liposomal amphotericin B (8.4 percent) and 544 infusions of conventional amphotericin B (19.0 percent, $p<0.001$); infusion-related reactions without fever occurred after 746 infusions of liposomal amphotericin B (23.7 percent) and 1776 infusions of conventional amphotericin B (62.2 percent, $p<0.001$). Among the documented cardiorespiratory events, there was a significantly lower incidence of hypertension, tachycardia, hypotension, and hypoxia in recipients of liposomal amphotericin B than in recipients of conventional amphotericin B. Only 1 patient receiving liposomal amphotericin B but 22 patients receiving conventional amphotericin B had documented hypoxia (measured predominantly by pulse oximetry) ($p<0.001$).

Reflecting the reduced frequency of infusion-related reactions in patients receiving liposomal amphotericin B, these patients were significantly less likely to receive acetaminophen, diphenhydramine, meperidine, hydrocortisone, or lorazepam to prevent such reactions (Table 3).

Nephrotoxicity and Hepatotoxicity

Significantly fewer patients receiving liposomal amphotericin B had nephrotoxic effects, as indicated by the doubling or tripling of the serum creatinine level ($p<0.001$) (Table 4) or by peak serum creatinine values above 3.0 mg per deciliter (265 μmol per liter); such levels occurred in 8 percent of those receiving liposomal amphotericin B, as compared with 18 percent of those receiving conventional amphotericin B ($p<0.001$).

Moreover, there was a reduction in hypokalemia (P=0.02), as well as a trend toward a reduction in hypomagnesemia (P=0.12), inpatients receiving liposomal amphotericin B, as compared with those receiving conventional amphotericin B. There was no significant difference in the frequency of hepatotoxicity in the two treatment groups.

Severe adverse events

The frequency of all severe adverse events (grade 3 or 4) and of severalspecific severe events (fever, chills, dyspnea, nausea, and vomiting) was significantly lower in the recipients of liposomal amphotericin B (Table 4). There was no significant difference between the groups in the frequency of hyperbilirubinemia.

Table 1: Distribution of patients according to age and sex

Age (years)	Male	Female	Total no. of patients
<30	6	5	11
31-40	20	15	35
41-50	80	60	140
51-60	130	106	236
61-70	120	40	160
>70	14	4	18
	370	230	600

Table 2: Distribution of patients according to comorbidity

Comorbidity	No. of patient
DM type II	480 (80%)
Hypertension	210(35%)
Ischemic heart disease	42(7%)
Hypothyroidism	12(2%)

Chronic kidney disease	36(6%)
None	30(5%)

Table 3: Measures of Success of Systemic Antifungal Therapy with Liposomal Amphotericin B or Conventional Amphotericin B

Measure	Liposomal Amphotericin (N=300)		Conventional Amphotericin B (N=300)	
	No.ofPatients (CI)	Success Rate(95% CI)	No.ofPatients	Success Rate (95% CI)
Overall success	142	47.3(43-56)	140	46.6 (44-55)
No breakthrough fungalInfection	279	93(86-94)	278	92.6 (85-94)
Survived 7 days afterinitiation of study drug	260	86.6(82-90)	254	84.6 (83-92)
Study drug notprematurely discontinued because of toxicity orlack of efficacy	254	84.6(82-89)	244	81.3 (77-85)

Table 4: Infusion-Related Reactions to Liposomal Amphotericin B and Conventional Amphotericin B

Effect	LiposomalAmphotericin B (N=300) No.(%)	ConventionalAmphotericin B (N=300) No. (%)
Reactions on day 1		
Fever following infusion (increase of »1.0°C)	51 (17)	140 (46.6)
Chills or rigors	55 (18.3)	165 (55)
Nausea	42 (14)	40(13.3)
Vomiting	16 (5.33)	22(7.33)
Other	52 (17.3)	76(25.3)
All reactions		
Chills	102 (34)	196 (65.3)
Nausea	95 (31.6)	94 (31.3)
Vomiting	42 (14)	71(23.6)
Headache	28(9.33)	29(9.6)
Flushing	18 (6)	2(0.6)
Tachycardia	8 (2.66)	43(14.3)
Hypertension	8 (2.66)	39(13)
Dyspnea	16 (5.33)	25(8.3)
Hypotension	12(4)	26(8.66)

Table 5: Effect of Liposomal Amphotericin B and Conventional Amphotericin B in Terms of Nephrotoxicity, Hepatotoxicity and Severe (Grade 3) or Life-Threatening (Grade 4) Toxic Reactions

Effect	LiposomalAmphotericin B (N=300)	ConventionalAmphotericin B (N=300)
Serum creatinine during therapy		
>1.5 times base-line value	94(31.3)	160 (53.3)
>2.0 times base-line value	54(18)	112 (37.3)
>2.0 times base-line value	24(8)	54(18)
Nephrotoxicity with concomitant nephrotoxic drugs		
0 or 1 drug	5(1.6)	14(4.66)
>2 drugs	49(16.3)	102 (34)
>3 drugs	32(10.6)	48(16)

Hypokalemia	21(7)	40(13.3)
Hypomagnesemia	59 (19.6)	80(26.6)
Hepatotoxicity	57(19)	70(23.3)
Grade 3 or 4 toxicity	24(8)	58(19.3)
Fever	35 (11.6)	128(42.6)
Chills	12(4)	25(8.33)
Nausea	4(1.33)	19(6.33)
Vomiting	25(8.33)	29(9.66)
HyperbilirubinemiaDyspnea	20(6.66)	34(11.3)

Discussion

This study comparing liposomal amphotericin B with conventional amphotericin B assystemic antifungal therapy in patients with Mucormycosis demonstrated that the treatments had similar overall success rates according to our composite score. However, liposomal amphotericin B was more effective in reducing the frequency of proved breakthrough fungal infections, infusion-related toxic reactionsand nephrotoxic effects.Hospital costs from first dose were significantly higher for all patients who received liposomal amphotericin B.

Few of the patient below 30 years of age has developed mucormycosis post Covid-19 infection. It can be attributed to their immunity and less incidence of comorbidity in young adults. Maximum no. of patients belong to age group of 51–60 years. It may be due to comorbidity associated with age. Mean age was 56 years with male to female ratio of 1.60/1. Similar results were reported by White *et al.*[3] in his study of 135 adults with median age 57 years and male to female ratio 2.2/1.

This study established that liposomal amphotericin B has significantly less infusion-related toxicity than conventional amphotericin B. The statistical strength of these observations is supported by the prospective and blinded bedside monitoring of more than 6000 infusions. The significant reduction in cardiorespiratory events in the group assigned to liposomal amphotericin B was especially encouraging. These benefits may be important in seriously ill patients who have poor tolerance of adverse cardiorespiratory events. Moreover, the reduction in infusion related toxicity may improve the quality of life in high risk patients.

Although lipid formulations of amphotericin B may cause respiratory distress, such events were less common among patients receiving liposomal amphotericin B than among those receiving conventional amphotericin B[4, 5].

Patients receiving liposomal amphotericin B had better sustained glomerular and tubular function than those receiving conventional amphotericin B, as evidenced by the lower rates of azotemia and hypokalemia.

Several mechanisms may contribute to the reduced nephrotoxicity of lipid formulations of amphotericin B. Among them are liposome-mediated selective transfer of amphotericin B to fungal cell membranes as compared with mammalian cell membranes; reduced levels of amphotericin B in the kidney in relation to the high levels achieved in the reticuloendothelial system; preferential binding of liposomal amphotericin B to high-density lipoproteins, as compared with conventional amphotericin B, which is bound to low-density lipoproteins; and selective local release of amphotericin B directly onto the fungal cells[6-11]. The toxicity of infusions of conventional amphotericin B is related to the release of tumor necrosis factor a, interleukin-1and interleukin-6 from monocytes and macrophages. Encapsulation of amphotericin B by the liposomal structure attenuates the release of these proinflammatory cytokines[12, 13].

As patients at higher risk undergo intensive chemotherapy and bone marrow or stem-cell transplantation, invasive fungal infections will continue to pose a threat to their successful treatment. This study demonstrates that liposomal amphotericin B is an appropriate alternative

to conventional amphotericin B for systemic antifungal therapy and that its use may reduce the frequency of breakthrough fungal infections, preserve renal function, and reduce the frequency of acute infusion-related toxic effects.

Diabetes mellitus type II is most common predisposing factor accounting for 80% cases. Similarly,Yohai*et al*. [14] and Ferry *et al*. [15]have found diabetes mellitus type II to be the most common predisposing factor. Hypertension and Ischemic heart disease were found in 35% and 7% patients respectively. Immunosuppression due to underlying disease is mainly responsible for secondary infections. Biopsy proved to be gold standard for diagnosis ofmucormycosis. Amphotericin B is the gold standard in the treatment of mucormycosis. The survival rate of patients dramatically has increased to the 60% after the introduction of Amphotericin B [16]. Liposomal amphotericin B is the first choice of treatment in patients with intracranial extension as it crosses the blood-brain barrier more effectively. Most of the patients respond well with Amphotericin B either conventional or liposomal, depending upon the renal status of the patient.

All patients in our study underwent surgical debridement[17]. Control of underlying disease, systemic antifungal medication and surgical debridement proved to be the mainstay of mucormycosis treatment.

Conclusion

Immune dysregulation caused by COVID 19 infection in addition to widespread use of steroids and broad-spectrum antibiotics may lead to the development mucormycosis. Diabetes Mellitus type II is another important risk factor and the presence of both have additional effect in causing mucormycosis.Early diagnosis can significantly improve prognosis.Liposomal amphotericin B is as effective as conventional amphotericin B for empirical antifungal therapy in patients with mucormycosisand it is associated with fewer breakthrough fungal infections, less infusion-related toxicityand less nephrotoxicity.

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