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EFFICACY OF COMBINATION THERAPY OF AMPHOTERICIN AND POSACONAZOLE IN TREATMENT OF MUCORMYCOSIS

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ABSTRACT

Background: Mucormycosis is an opportunistic systemic fungal infection which is debilitating caused by order Mucorales. The standard management of mucormycosis consists of aggressive debridement of the infected tissue and parenteral anti-fungal therapy with Amphotericin B. Liposomal amphotericin B is a "true" liposomal formulation of amphotericin B with greatly reduced nephrotoxicity and minimal infusion-related toxicity. Very minimal data is available on the usefulness of combining different antifungal agents for an effective outcome. Our study was undertaken at a time when there was a huge turnover of mucormycosis cases during Covid 19 pandemic with resultant shortage of important resources including liposomal amphotericin B. In effect, combination of liposomal amphotericin B with posaconzole gave a promising outcome. **Objectives:** To study the efficacy of combination therapy of liposomal amphotericin B and posaconazole in the treatment of mucormycosis. **Methodology**: It is a prospective study of 43 patients with mucormycosis who received combination therapy based on their disease severity. **Results:** In our study, 16 (37%) were considered as patients with mild disease, 18 (41.8%) were considered as patients with moderate disease and 9 patients (20.9%) were considered as severe. 20 (58%) patients out of 34 patients with mild to moderate disease showed improvement after combination therapy. **Conclusion**: A significant percentage of patients in our study showed improvement with combination therapy of liposomal amphotericin B and posaconazole in terms of survival and disease recurrence.

INTRODUCTION

Mucormycosis is an opportunistic systemic fungal infection caused by the order Mucorales. The pathogens are commonly found in the environment within the soil and decaying organic debris that can enter human body by inhalation. It has been classified according to its clinical presentation into rhino-cerebral, cutaneous, gastrointestinal, pulmonary and disseminated forms [1]. Till date, in India 28,252 occurrences of mucormycosis or black fungus has been documented in 28 states and union territories. Because of the high mortality associated

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with this infection, effective treatment requires early detection and recovery from predisposing factors [2]. In India, COVID 19 associated outbreak of mucormycosis occurred as an epidemic during the second wave of COVID 19. Management of mucormycosis consists of treatment of immunocompromised state, aggressive debridement of the infected hard and soft tissue and systemic antifungal therapy with Amphotericin B [3]. Posaconazole is a new extended –spectrum azole antifungal that has demonstrated in-vitro and in-vivo activity against zygomycetes. Like other azoles, posaconazole inhibits sterol 14 alpha–demethylation, resulting in faulty cell membrane synthesis [4]. Amphotericin B remains the gold standard for the treatment of invasive fungal infections. However, its efficacy is limited with response rates ranging from 10% to 80 %. Moreover it is known for its nephrotoxicity [5]. This paper highlights the effectiveness of combination therapy of liposomal amphotericin B (L-AMB) and posaconazole in sinonasal and rhino-orbital mucormycosis.

MATERIALS AND METHODS

Study design

Prospective institutional based study. Institutional ethical committee clearance taken.

Patient selection

1. All covid and post-covid patients with suspected mucormycosis who have received Injection Liposomal amphotericin B.
2. All diagnosed cases of mucormycosis who have received injection Liposomal Amphotericin B and Tab Posaconazole.

Patients who have discontinued the treatment were excluded. This is a prospective study conducted on 43 patients with covid and post covid who presented to McGann District hospital, Shimoga between May 2021-August 2021.Patients presenting with symptoms of headache, nasal obstruction, facial swelling, eye pain and eye swelling were evaluated as suspected cases of mucormycosis. All these patients were evaluated holistically by Otorhinolaryngology department along with Department of Medicine, Ophthalmology, Neurology, Anaesthesia and Dentistry. Microscopic examination by fungal mount and fungal culture of swabs from nasal cavity were done for all patients. These patients were radiologically evaluated with computed tomography (CT) and MRI scans of paranasal sinuses, orbit and brain. These patients were diagnosed based on high index of clinical suspiscion or the following investigations such as

- Diagnostic nasal endoscopy showing blackish crusts
- Positive KOH mount or fungal culture
- Radiological features consistent with zygomycosis infection
- Histopathology of biopsy from nasal cavity tissue or crusts showing presence of predominantly aseptate (pauci-septate) wide, ribbon-like hyphae, presence of tissue necrosis and angio-invasion.

This study was conducted on 43 patients who received anti-fungal therapy. They were classified as mild, moderate and severe based on the extent of disease involvement.

- Mild – Sino-nasal mucormycosis.
- Moderate – Sino-nasal mucormycosis with orbital involvement or palatal involvement
- Severe – Rhino-cerebral mucormycosis

Patients with sino- nasal mucormycosis were treated primarily with surgical debridement and Inj. liposomal amphotericin B 2mg/kg/day for 2 weeks post operatively and then switched over to oral Tab Posaconazole 300mg BD on day 1 followed by 300mg OD for 3 months. Patients with rhino-orbital or palatal mucormycosis were treated with combination therapy of Inj. liposomal amphotericin B for 2-4 weeks post operatively and Tab Posaconazole 300mg OD for 3 months.

Following diagnosis and initiation of treatment, patients were regularly monitored for haematologic and renal parameters every 2nd day such as

- Complete blood count
- Renal function tests
- Serum electrolytes

Blood sugars were monitored and managed accordingly with 8^{th} hourly blood glucose level measurements and regular Physician reviews. Potassium chloride infusions to treat hypokalaemia were given for patients who developed reactions to systemic antifungal therapy. Following injection liposomal amphotericin, few patients developed reactions in the form of fever, chills, hypokalaemia and deranged renal function tests. Mild symptoms were treated with analgesics. In patients with severe reactions, other antifungal agents such as injection lipid complex amphotericin and injection Posaconazole were given and withstood.

Adjunctive therapies like amphotericin gel was used to smear the post-operative cavities to reduce local recurrence. Extensive post

total /subtotal maxillectomy cavities were routinely debrided. Regular methylene blue sinus wash and amphotericin-soaked ribbon gauze packing of cavities were done.

Mild disease

16 out of 43 cases with sino-nasal involvement were grouped with mild disease. These patients underwent bilateral functional endoscopic sinus surgery and were started on Injection liposomal amphotericin B alone in varied dosages i,e 1-3mg/kg/day on admission and continued post operatively for 2 weeks. These patients were subsequently started on Tab. Posaconazole 300mg OD for 3 months. Patients were assessed post operatively for the following:

1) Requirement of second surgery
2) Local recurrence of disease
3) Progression of disease to involve eye/palate or cerebral extension.

Moderate disease

18 out of 43 cases were categorized as moderate disease with orbital/ palatal involvement. 6 out of 18 patients underwent radical surgeries such as total/subtotal maxillectomy with orbital exenteration. These Patients were started on Injection amphotericin 1-3mg/kg/day for 2-4 weeks. Injection Posaconazole was given to 3 patients who did not tolerate amphotericin. These patients were subsequently started on Tab Posaconzaole 300mg OD for 3 months.

These patients were assessed for effectiveness of combination therapy in the form of

1) Local control of disease
2) Requirement of second stage surgery
3) Radiological improvement

Further progression of disease was assessed by regular endoscopic examination & radiological investigation for 3 months.

Severe disease

Patients with rhino-cerebral mucormycosis with co-morbidities were categorized as severe. All patients were given Injection Liposomal Amphotericin B 5mg/kg/day for 3-4 weeks and then with Tab. Posaconazole 300 mg.

RESULTS

In our study, out of 43, 16 were mild, 18 were moderate and 9 were classified as severe disease.

Table 1: Severity of disease

Disease category	Number of patients
Mild	16
Moderate	18
Severe	9

Mild disease

Out of the 16 patients, 2 required second stage procedure due to progression of disease to involve palate/orbit and started on combination therapy. 6 patients improved with injection liposomal amphotericin B and later Tab. Posaconazole 300mg. Out of the 16 cases, 1 death was reported due to COVID-19 related complications, 1 patient required neurosurgical intervention due to intracranial extension and 6 patients did not give consent for continuation of treatment. (Figure 1)

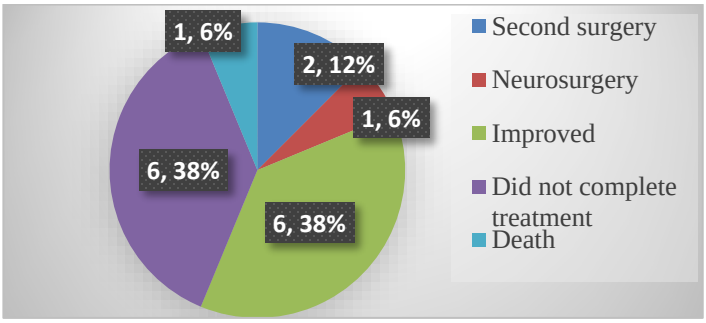

Figure 1: Outcomes of patients with mild disease

Moderate disease

Among the 18 patients grouped with moderate disease, 8 patients who underwent surgery improved with injection amphotericin for 3 weeks followed by Tab. Posaconazole 300mg OD for 3 months. 6 out of 18 patients underwent second stage procedure due to progression of disease to involve palate/orbit, 5 among these 6 patients improved with subsequent combination therapy and 1 patient was lost to follow up. 2 patients did not tolerate Inj. liposomal amphotericin B during the 2nd week and developed hypokalaemia. These patients were switched over to Inj. Posaconazole for 3 weeks and then oral Posaconazole 300mg OD for 3 months. Out of the total 18, 4 deaths were reported due to post - Covid complications. Out of the total 18 patients, we observed that 13 patients improved with combination therapy. (Figure 2)

Severe disease

Among the 9 patients with severe disease, 2 patients showed improvement with injection liposomal amphotericin B. 4 patients were referred for neurosurgical intervention, 1 patient

was lost to follow up. 2 mortalities were reported due to dissemination of mucormycosis and associated co-morbidities (Figure 3)

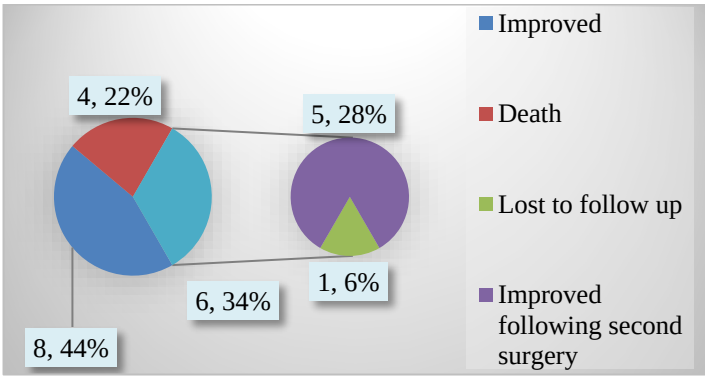

Figure 2: Outcomes of patients with moderate disease

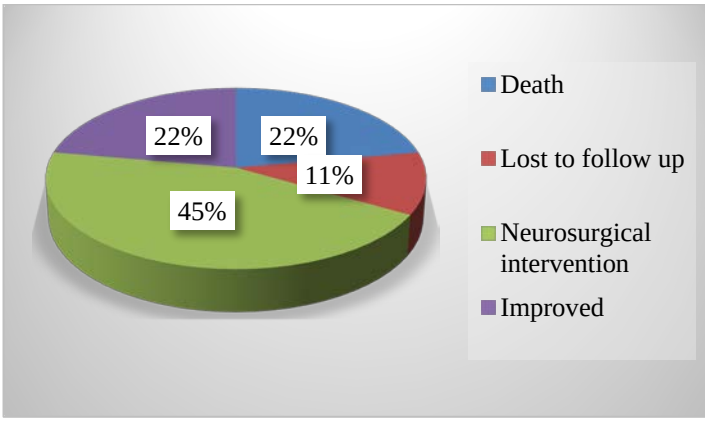

Figure 3. Outcomes of patients with severe disease

DISCUSSION

It is well known that early initiation of treatment in mucormycosis is essential for better outcomes.

Optimal management include rapid diagnosis, treatment of underlying risk factors, antifungal therapy and extensive surgical debridement. First line of treatment is systemic amphotericin B. However due to heavy load of mucormycosis cases during the Covid 19 pandemic, we encountered an acute shortage of liposomal amphotericin B. Different centres used various combinations of anti-fungal agents with varying results. Based on the limited available literature, we tried a combination of liposomal amphotericin B with Tablet Posaconazole with satisfactory results.

Members of the polyene class of antifungals, such as amphotericin B deoxycholate (AmB) or its lipid derivatives have demonstrated activity against mucormycosis. The optimal dosages for treatment of mucormycosis is not yet fixed for any antifungal agent. Total duration of therapy for mucormycosis should be individualized for each patient. The response of mucormycosis to antifungal agents is host and site dependent[6]. Amphotericin B and its lipid formulations such as liposomal, lipid complex and colloidal dispersion have improved therapeutic indexes when compared to conventional amphotericin[7]. The adequate dosage of these drugs when treating mucormycosis is dependent on the disease areas and the patient's condition[5]. The standard daily dose of liposomal AMB suggested by current guidelines is 5 mg/kg/day. Efficacy of liposomal AMB was dose-dependent: a dose of 10 mg/kg/day has been proved to be more effective in reducing fungal burden compared to 1 or 5 mg/kg/day[7]. In a study by Gleissner et al, out of 120 cases of mucormycosis with hematological malignancies, treatment with liposomal amphotericin B demonstrated 67% survival rate and a survival rate of 39% with amphotericin B deoxycholate[8].

Triazoles are a class of antifungals that act by inhibiting ergosterol synthesis from the fungal cell membrane**.** New triazoles such as posaconazole and isavuconazole exhibit higher activity against mucorales in vitro than other triazoles[7]. Posaconazole is a second-generation triazole with broad-spectrum antifungal activities. This drug is currently available in the following three formulations: suspension, delayed-release tablet, and injection. Posaconazole has varying activity against Mucorales and it appears that the drug's effectiveness is species dependent[9]. Minimum inhibitory concentration (MIC) of posaconazole for various Mucorales species varied widely between 1.0 and 8.0 µg/mL. Serum concentration higher than 4000 µg/mL is needed to suppress the growth of Rhizopus species with an MIC of 2 µg/mL[3].In patients with preexisting kidney complications, first-line treatment with intravenous administration of isavuconazole or posaconasole is recommended[10]. Sachin Rai et al in their study concluded that posaconazole can be used for the treatment of rhinomaxillary mucormycosis in immunocompetant patients[11] In a salvage study by Greenberg et al, they observed an overall success rate of 79% in terms of survival in response to posaconazole in 24 patients with zygomycosis [4].

A combined therapeutic approach has benefits such as synergistic effects of the drugs and a broader coverage against pathogens compared to monotherapy.Rodriguez et al in their

study on murine mucormycosis observed that there was no advantage of combination studies over amphotericin monotherapy[12]. In a study by Ibrahim et al on mice with neutropenia or diabetic ketoacidosis and mucormycosis they observed that combination of posaconazole and L-AmB did not improve survival, compared with L-AmB monotherapy[13]. Van Burik et al reported 60% response rates with posaconazole (45% partial response, 15% complete response) for salvage therapy in patients with mucormycosis who were refractory to or intolerant of amphotericin B[14]. A systemic review by Cornely et al suggested that Posaconazole is a second line of drug and can be used as salvage therapy following the amphotericin B therapy[15]. In our study patients with moderate disease, who received injection amphotericin 1-3mg/kg/day for 3 weeks and Tab. Posaconazole 300mg OD for 3 months showed a recovery rate of 72% . Among the 16 patients categorised as mild disease,8 eligible patients showed improvement (100%). Of the remaining 8 patients, 6 did not give consent for further treatment, 1 patient expired and 1 patient was referred for neurosurgical intervention.

CONCLUSION

In our study, combination therapy was found to be effective in mucormycosis patients with mild and moderate disease. It showed better patient compliance towards treatment, lower incidence of adverse effects which occurred due to systemic amphotericin alone and is cost effective. Combination therapy of amphotericin and posaconazole improves survival and reduces local disease recurrence. Therefore, combination therapy will contribute significantly in reducing absolute dependency on amphotericin for treatment of mucormycosis. However, a larger study with varied doses of liposomal amphotericin B and posaconazole is required to conclusively prove the efficacy of combination therapy.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Gangadhara KS, Shridhara S contributed as Operating Surgeons for all cases. Ramesh S, Nandini P contributed in collecting data and Drug monitoring. Gayatri Jayan contributed in data compilation and preparing draft of manuscript. All the author contributed in proofreading and reviewing the manuscript.

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