

# Retrobulbar Amphotericin B in Mucormycosis: A Ray of Hope

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**Aim:** The aim of the study was to study the role of Retrobulbar Amphotericin B in patients with Mucormycosis.

**Methods:** The retrospective study conducted on 86 cases at a tertiary care hospital analyzed detailed history, examination and management options. The staging was done on basis of clinical and radiological examination. Management included functional endoscopic sinus debridement followed by lavage with Liposomal Amphotericin B. The patients with ocular involvement were subjected to Exenteration or Retrobulbar injections of Amphotericin B (3.5 mg / ml) based on the disease staging.

## Abstract

**Results:** Most common risk factors were steroid intake (89.5 %) and Diabetes (87.2%). Seventy four eyes of 71 patients had ocular involvement out of which 20 eyes (27.0%) of 19 patients (26.7%) presented with no perception of light. Seven patients were subject to exenteration of globe and 58 eyes were given Retrobulbar injections (Mean number of injections =  $5.58 \pm 2.36$ ). The mean best corrected visual acuity of  $0.769 \pm 0.935$  logMar did not deteriorate ( $p=0.871$ ) post treatment. The mean restriction of extraocular movements were  $2.32 \pm 1.09$  which improved to  $1.56 \pm 1.56$  ( $p=0.0031$ ) following retrobulbar injections.

**Conclusion:** The patients of Mucormycosis without cerebral involvement can be subjected to Retrobulbar Amphotericin B injections that can control the ocular manifestations and stabilise the vision thus saving the globe..

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**Keywords:** Amphotericin B, Covid, Exenteration, Mucormycosis, Retrobulbar Injection

## Introduction

The pandemic of Covid infection affected majority of population in its second wave. The trailing end of the pandemic lead to another epidemic; Mucormycosis in developing nations like India.<sup>1,2</sup> It's an angioinvasive disease caused by saprophytic fungi of the order Mucorales whose main pathogenic feature is tissue infarction and necrosis.<sup>1-3</sup>

The exact incidence is unknown due to lack of population based studies but the estimated prevalence in India is 70 times higher in comparison to developed nations which were estimated to be at 0.02 to 9.5 cases (with a median of 0.2 cases) per 100,000 persons.<sup>3,4</sup> Annual incidence reported is of 12.9 cases per year during 1990–1999, 5 35.<sup>5</sup> cases per year during 2000–2004 6 cases per year during 2000–2004 6 1999, 5 35.<sup>6</sup> cases per year during 2000–2004,<sup>6</sup> and 50 cases per year during 2006–2007.<sup>7</sup> The overall numbers increased from 25 cases per year (1990–2007) to 89 cases per year (2013–2015).<sup>8</sup>

Rhino-Orbito-Cerebral-Mucormycosis (ROCM) is the most common form reported from India in contrast to developed nations where most common form is pulmonary mucormycosis.<sup>1,4</sup> The tissue infarction and necrosis of retro-orbital space and subsequent Orbital Apex Syndrome lead to various ophthalmic manifestations including total ophthalmoplegia, proptosis, loss of vision etc.<sup>1,2,8</sup>

The most common causes reported in previous studies have been Diabetes Mellitus, haematological malignancy and chemotherapy, haematopoietic stem cells, and solid-organ transplant recipients on immunosuppressive therapy, patients on long-term steroid, patients with iron overload, patients on peritoneal dialysis, extensive skin injury/burn, human immunodeficiency virus (HIV) infection, and voriconazole therapy.<sup>1,2,8</sup>

The main aim of the study was to find out the demography, risk factors and the role of Retrobulbar Amphotericin B (RAMB) in patients with biopsy proven Mucormycosis.

## Material & Methods

The study participants were 86 cases of biopsy confirmed Mucormycosis admitted at a tertiary care hospital in North India. The participants were subjected to written & informed consent for all the procedures performed. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Study design:** It was a retrospective study done on the patients admitted in dedicated ward for Mucormycosis after the confirmed biopsy report.

Detailed history and examination was recorded from the bed head tickets (BHT) for all the patients done by dedicated team of doctors that included Otorhinologists, Ophthalmologists, Physicians, Radiologists & Neurologists. All the findings were noted from the BHTs of the patients and entered in an excel spread sheet by a dedicated person. The diagnosis was confirmed by KOH mount of nasal swab and tissue biopsy taken from the effected turbinate of the patients that was sent to microbiology lab of the institution.

Blood investigations that included complete blood count (CBC), inflammatory markers, renal function tests, liver function tests and serum electrolytes were analyzed at admission, two weeks and 4 weeks after admission. (Contrast enhanced MRI was done for all patients with regards to involvement of paranasal sinuses (PNS), orbit and brain done at the time of admission and 3 weeks after admission).

The patients were subjected to endoscopic sinus debridement followed by injection of liposomal Amphotericin B lavage by Otorhinologists after confirmation of diagnosis. Immediately after confirmation of diagnosis injection liposomal Amphotericin B (5 mg/kg/day) was initiated for the patients with Rhino-Orbito-Mucormycosis (ROM) and dose of 10 mg/kg/day was started in patients with ROCM for infection of the central nervous system.

The patients with eye involvement were categorized by Staging of ROCM published by Sen M, Honavar SG et al.<sup>9</sup> The subjects with ROM without cerebral involvement or without risk of cerebral involvement were subjected to Retro-orbital Amphotericin B (RAMB) injection (3.5 mg/ml in 1 ml). The subjects with 3a and 3b staging were given alternate day RAMB and stage 3c were given daily injections till 5 doses. The RAMB were repeated on the basis of clinical response and were followed up both clinically and by imaging. The photographs taken were analyzed to document the regression of signs especially ocular movements in 9 gazes, proptosis, ptosis and Best Corrected Visual Acuity (BCVA.)

The patients with 3d staging were assessed with regards to cerebral involvement by neurologists. These patients with ROCM were subjected to exenteration along with lavage of orbital cavity by Amphotericin B injection along with endoscopic sinus debridement surgery.

Five patients died during due course of treatment who were admitted with cerebral involvement and/or brain abscess. Four patients left against medical advice (LAMA) so their follow up examination could not be included in the data analysis.

All the data were entered in Microsoft excel spread sheet and the statistical analysis was done by Statplus software AnalystSoft Inc (version V7, 2021). The mean and standard deviation were calculated by descriptive statistics. Two tailed p value ( $p < 0.05$ ) was taken as significant after calculation of mean difference from paired 't' test.

## Results

Total of eighty six post covid patients were admitted and were found to have biopsy confirmed Mucormycosis report (Table 1). There were 61 males (70.9%) and rest were females. Mean age was  $52.164 \pm 13.1$  years (Median = 52 years).

Total of 75 patients (87.2%) were having Diabetes Mellitus (mean Hb1Ac =  $8.98 \pm 2.98$ ) out of which 23 patients (30.6%) were on insulin. The next common systemic illness was hypertension in 47(54.6%) patients followed by hypercholesterolemia in 23 (26.7%) patients.

The history of vaccination revealed that only three patients (3.4%) were immunised by single dose of Covishield vaccine (Oxford-AstraZeneca, SII, Pune, India). Rest of the patients did not take even a single dose of vaccine.

Thirty three patients (38.3%) were hospitalised for the treatment of Covid, out of which 27 (81.8%) were given oxygen during their hospital stay. Rest all patients were treated at home. The mean duration of presentation to hospital with symptoms of Mucormycosis after Covid negative report was  $9.5 \pm 4.98$  days (Medium = 10 days, Range 0 to 20 days)

Seventy patients (89.5%) took steroid medications for their treatment of Covid infection, out of which 31 patients (43.6%) were put on injectable steroids.

The mean BCVA of all patients at admission was  $0.518 \pm 0.881$  log MAR units that changed to  $0.515 \pm 0.857$  log MAR units ( $p = 0.90$ ) after 3 weeks of treatment. Fifteen patients

(17.4%) were found to have no eye involvement clinically and radiologically. Three patients out of 71 patients (82.5%) with ocular involvement had bilateral signs. Therefore, 74 eyes of 71 patients, out of 20 eyes (27.0%) of 19 patients (26.7%) presented with no perception of light (PL negative). Amongst these 20 eyes, three eyes of 2 patients presented with blindness due to Central Retinal Artery Occlusion (CRAO). Another patient had lost vision due to optic neuritis and rest of the eyes (16 eyes of 16 patients) presented with orbital apex syndrome.

The Mean BCVA of the patients with eye involvement (excluding patients with PL negative vision) were  $0.769 \pm 0.935$  log Mar units that changed to  $0.734 \pm 0.928$  log MAR units at 3 weeks ( $p=0.871$ ) post treatment it remained unchanged at 6 weeks post treatment.

Mean intraocular pressure (IOP) was  $17.7 \pm 8.3$  mm Hg in the affected 74 eyes of 71 patients at the time of admission and  $14.7 \pm 4.35$ . ( $p=0.195$ ) 3 weeks post treatment. Four patients had raised IOP for which antiglaucoma medication was started. The mean IOP in unaffected eyes of the 68 patients (as 3 patients had bilateral involvement) was  $15.35 \pm 4.2$  mm Hg. The difference between affected and unaffected eye was  $2.35 \pm 4.1$  mm Hg ( $p = 0.303$ )

[The involvement of extraocular muscles on clinical examination was assigned numbers according to the restriction of movement of eye. One number was assigned for one muscle involvement (movement restriction in one direction) and number 4 was assigned for 4 muscles involved and 5 was assigned for restriction of movements in all the gazes (total ophthalmoplegia)]. The mean restriction of ocular movement in the 74 eyes of 71 patients were  $2.74 \pm$  units 1.37. Complete ptosis was present in 15 (20.2%) and partial ptosis was present in 17 (22.9%) out of 71 patients.

The staging of the disease showed maximum patients in Stage 3b, done as per involvement on contrast enhanced MRI of orbit (Figure 1).<sup>9</sup>

The mean restriction of ocular movements in the patients who were given RAMB (58 eyes) were  $2.32$  units  $\pm$   $1.09$  units. The patients who underwent exenteration (7 in numbers), expired (5 in nos) and LAMA (4 in numbers) were excluded to get a total of 58 eyes receiving RAMB. The mean number of

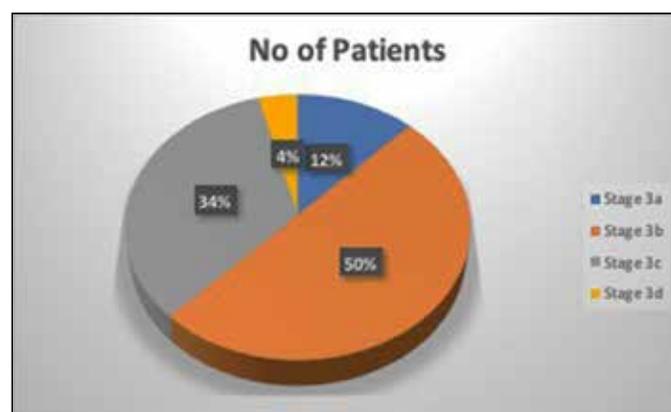


Figure 1: Staging of ocular manifestations on basis of contrast enhanced MRI in patients with Mucormycosis

RAMB injections given were  $5.58 \pm 2.36$  (range 3 - 15) which lead to improvement in mean ocular restriction (Figure 2) to  $1.56 \pm 1.56$  from  $2.32 \pm 1.09$  ( $p=0.0031$ ).

The complete ptosis improved in 9 out of 15 (60%) patients (Figure 3) and partial ptosis improved in 13 out of 17 (76.4%) patients (Figure 4). Two patients of 7 exenterated eyes were given 3 RAMB before exenteration but no improvement in the clinical status lead to the decision for exenteration. All

The mean age revealed that maximum number of cases were in the age group of 30-45 years (36%) followed by 45 - 60 years (33.7%). Males were more than the females which appear to be by chance due to a small sample size. Most common systemic associations were reported in Diabetes Mellitus and systemic steroid intake as is seen with other studies too.<sup>1,2,11,12</sup>

The history of hospitalization for Covid infection was found



Figure 2: Nine gaze ocular movements pre RAMB Injection and post RAMB injection showing decreased periorbital ecchymosis and improved ocular movements



Figure 3: Improvement in complete ptosis after RAMB injections

the patients who underwent exenteration, survived and were discharged satisfactorily. Patients were discharged on Posaconazole tablet (300 mg twice daily on day one followed by once daily dosing).

**Discussion**

The upsurge in the cases of Mucormycosis post Covid infection lead to another epidemic in the ongoing pandemic.<sup>10-11</sup> The panic rose due to high incidence of mortality and morbidity due to loss of eyes/vision and posed a great challenge in management of these cases.<sup>12</sup>

in only one third of cases so, it can't be included as a major risk factor. The median time of presentation was 9 days (maximum 20 days) after covid negative report emphasizing that second week post covid infection is the most crucial for presentation of Mucormycosis.

The history of vaccination revealed that only 3.4% percent were vaccinated by single dose of vaccine and rest all were not vaccinated. Emphasising the fact that probably the vaccine provided sufficient immune protection to covid survivors so that immunity levels of individuals didn't



**Figure 4:** Improvement in partial ptosis, proptosis & conjunctival chemosis post RAMB injections

decline to the levels that post Covid complications like secondary infections can affect them.<sup>13-15</sup> Although a larger sample size with other infections should be considered to say these facts conclusively.

The management protocol included debridement by functional endoscopic sinus surgery (FESS) by Otorhinologist, that remained the mainstay in all patients followed by daily Liposomal Amphotericin B injection.<sup>11-13</sup> The patients with eye involvement were given RAMB as per the protocol described in the material and methods.<sup>11</sup> The RAMB injections have been reported in some sections sporadic case reports<sup>16-18</sup> but this is one of the largest series of patients receiving RAMB and responding positively to it. The RAMB also proved to be effective in restoring the ocular movements ( $p=0.0031$ ) of the patients (figure 2) and also helped to restore the eyelid movements (figure 3 and 4). Therefore, the need for exenteration was reduced in majority of the patients. The patients with lost vision could not regain their visual acuity<sup>14</sup> but restoration of eyelids/ocular movements saved the eye and improved psychology due to preserved cosmesis for the patients.

The conclusion was drawn that post covid patients can present with deadly secondary infections like mucormycosis. The patients who present without cerebral involvement can be subjected to RAMB injections that can control the ocular manifestations and stabilise the vision of the patient and subsequently can save the globe of the patients. Although a randomised controlled trial / prospective study on larger number of subjects is requested to provide more conclusive results.

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