Original Research Article

A study on the ocular outcomes of transcutaneous retrobulbar administration of injection liposomal amphotericin-b in rhino-orbito- cerebral mucormycosis

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Abstract

Background: Rhino-orbito-cerebral Mucormycosis (ROCM) is an angio invasive fungal disease affecting the immunocompromised and patients with other debilitating diseases. There has been an exponential rise in its incidence post the second wave of COVID 19 in India, as the COVID infection itself acts as a risk factor along with others like uncontrolled Diabetes, over use of Zinc supplements, Oxygen therapy, usage of steroids. The fungus enters the Paranasal sinuses and from there spreads rapidly to Orbits, Maxilla, Orbital apex and Intracranial extension. **Materials and Methods:** 100 cases of Post COVID Rhino-orbito-cerebral Mucormycosis attending the Government General Hospital, Guntur were taken in this study, during the period of May 2021 to July 20th 2021. Appropriate history, clinical examination and all the required investigations were performed by a multi-speciality team of doctors. All the cases with proven fungal elements on biopsy or proven fungal invasion of Orbits/ Orbital apex/ Extraocular muscles/ Retrobulbar fat were administered Transcutaneous Retrobulbar Injection Liposomal Amphotericin-B(TRAMB) 3.5 mg/ml given for 4 doses and followed for a period of 1 week and depending on the clinical improvement, the doses are repeated. 100 cases were followed closely and the ocular findings were recorded and results are tabulated. **Results:** 100 cases of proven fungal etiology are followed after administering TRAMB for a minimum of 1 month. Of the 100 patients included in the study, 63 patients showed improvement in the ocular symptoms either resolution of Proptosis, ptosis, improvement in Visual acuity. 18 patients had neither improvement nor deterioration in ocular symptoms. 19 patients had deterioration in their ocular status despite the injections and thus are considered for either Exenteration/ Enucleation/ Evisceration depending on the orbital extension. 1 Exenteration, 9 Enucleations, 3 Evisceration are performed. Lateral Canthotomy and Cantholysis with Orbital lavage with Liposomal Amphotericin-B is done for 10 patients. **Conclusion:** Of the 100 cases given TRAMB, 63% of cases showed improvement in their symptoms. 18% cases had neither improvement nor deterioration. 19% of cases had deterioration in their ocular condition. Early diagnosis and intervention has resulted in better prognosis and improvement in ocular complaints. In patients with delay in the diagnosis or intervention led to intracranial spread and resulted in loss of vision for whom destructive ocular surgeries are performed to contain the further spread.

Keyword: Rhino-orbito-cerebral Mucormycosis (ROCM), Transcutaneous Retrobulbar Amphotericin-B injection (TRAMB), Proptosis, Ptosis, Mucormycosis, Liposomal Amphotericin-B, Functional Endoscopic Sinus Surgery (FESS).

Introduction

Mucormycosis (Black fungus- which is a misnomer) is a potentially lethal, angioinvasive fungal infection predisposed by diabetes mellitus, corticosteroids and immunosuppressive drugs, primary or secondary immunodeficiency, hematological malignancies and hematological The fungus that causes the disease is ubiquitous in nature and is found in soil and on decaying vegetation. Because the fungus is so widespread, humans are exposed to it on regular basis. The spores of the fungus are inhaled through the mouth and nose, but infection rarely occurs in a person with an intact immune system, because macrophages phagocytize the spores[1]

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stem cell transplantation, solid organ malignancies and solid organ transplantation, iron overload, etc. It is an aggressive opportunistic fungal infection, also known as Phycomycosis and Zygomycosis. It is caused by organisms of the family Mucoraceae (including the genera Mucor, Absidia, Rhizopus).

However, an immunocompromised individual is unable to mount an effective immune response against the inhaled spores; thus, germination and hyphae formation occur and infection develops, most commonly in the sinuses and lungs.

When the fungus invades the paranasal sinus mucosa, it may spread directly to the orbital apex and, from there, gain intracerebral access. It is difficult to diagnose early, as patients often present with non specific symptoms. By the time signs of orbital apex involvement develop, it is often too late to save the patient's vision, or even the patient's eye or life. The presentation is typically a rapidly progressive infection, and the disease is associated with a high mortality rate. It can affect other parts of the body such as the lungs and gastrointestinal tract[2].

The increasing incidence of Rhino-orbito-cerebral Mucormycosis

(ROCM) in the setting of COVID-19 in India and elsewhere has become a matter of immediate concern. Since February 2021, there has been an exponential increase in incidence in India, in sync with the soaring second wave of COVD19.

New corona virus SARS COV 2 itself may serve as a risk factor - chronic respiratory disease, corticosteroid therapy, intubation /mechanical ventilation, deranged glucose metabolism, which may lead to secondary fungal infection. Overall mortality in Pulmonary Mucormycosis: 50-70%, Rhinocerebral: 30 - 70%, CNS involvement: >80%, Disseminated: > 90%, AIDS: almost 100%.

Risk factors for development ROCM include

- Case of concurrent or recently (3weeks or high dose >1week), Tocilizumab, other immunomodulators, or therapy used with transplantation
- Prolonged neutropenia
- Uncontrolled Diabetes Mellitus
- Trauma, Burns, IV drug abusers
- Prolonged ICU stay
- Post-transplant/malignancy (solid or Hemopoietic)
- Voriconazole therapy
- Deferoxamine or other iron overloading therapy
- Contaminated adhesive bandages, wooden tongue depressors adjacent buildingconstruction hospital linens
- Renal failure, diarrhoea, and malnutrition in low-birth-weight infants/even children/adults

One of the probable cause for Mucormycosis in COVID is excessive use of zinc. Steroids areused in rheumatoid arthritis, vascular collagen disorder, interstitial pneumonia, glomerulonephritis, allergic condition of skin, connective tissue disorders, COPD since decades. But this black fungus (which is a misnomer, black colour is the due to tissue necrosis caused by fungus) was hardly seen. But in COVID, along with many other risk factors, excessive use of zinc acts as growth factor for Mucormycosis. In vitro study it has been seen that zinc chelator (zinc antidote) like clioquinol or phenanthrolene or other zinc chelators inhibit the growth of this fungus. Thus, zinc deprivement neutralises the growth, and also it is difficult to grow this fungus in zinc deficient tissue. Zinc chelator has been found to have Amphotericin B like action[3,4].

Patients with COVID-19 illness (active/recovered) presenting with the following symptoms

- Sinusitis: Fever, nasal stuffiness, facial pain and numbness, retro-orbital headache, hyposmia, blood-tinged/brownish black nasal discharge, Nasal mucosal erythema, inflammation, purple or blue discoloration, white ulcer, ischemia, or eschar
- Maxillary: Toothache, loosening of maxillary teeth, jaw involvement
- Eye symptoms: Redness and swelling of eye, diplopia (double vision), visual loss; Eyelid, periocular, facial discoloration, Sudden loss of vision, Sudden ptosis, Ocular motility restriction
- Regional pain – orbit, paranasal sinus or dental pain
- Facial paresthesias, anesthesia
- Facial palsy
- Fever, altered sensorium, paralysis, focal seizures

Stage 2	Involvement of Paranasal sinuses
Stage 3	Involvement of Orbit
Stage 4	Involvement of CNS

Type of study

A Prospective study

Place of study

Government General Hospital, Guntur

Aim

To study the ocular outcomes of TRAMB in patients with post COVID Rhino-orbito-cerebral Mucormycosis (ROCM).

Inclusion criteria

Included patients with symptoms and history suggestive of ROCM 2.Included patients with signs suggestive of ROCM

Exclusion criteria

Patients who are not willing to give consent 2.Patients with age less than 18 years 3.Patients who are negative for fungal biopsy

Diagnosis: Symptoms + Investigations Specific points to be observed in history

- H/o COVID infection (Immunosuppressive drugs/ Ventilatory care, etc.)
- Co morbid conditions: Diabetes mellitus/ Malignancy/ HIV/ Chronic kidney disease /Obesity/ Other systemic illness
- Local factors (H/O tooth extraction or any other oral/surgical procedure/ Head injury)

Investigations include

1. Lab parameters: CBC, ESR, FBS, PPBS, HbA1C, LFT, RFT with electrolytes, Viral markers(HIV/HBV/HCV)
2. Diagnostic nasal endoscopy: crusting, debris, scabbing, granulation, discoloured mucosa (either darkened or pale), decreased bleeding and insensate mucosa
3. CECT Nose and PNS: Erosion and thinning of bones, Enlargement of masticatory muscle, Mucosal thickening of sinuses Changes in Fat Planes
4. CEMRI Brain Orbit and Face: Optic neuritis, Intracranial involvement, Cavernous sinus thrombosis, Infratemporal fossa involvement
5. KOH staining & microscopy - Direct microscopy using fluorescent brightener and histopathology with special stains (e.g. PAS and GMS) Typical findings: non-septate/pauci- septate, ribbon-like hyphae (at least 6–16μm wide), Vessel occlusion
6. Histopathology- haemorrhagic infarction, coagulation necrosis, angioinvasion, infiltration by neutrophils (in non-neutropenic hosts), and perineural invasion.
7. Fungal culture- Routine media at 30°C and 37°C. Typical findings: cotton white or greyishblack colony

Proposed staging of ROCM

STAGE	CLINICAL FEATURES
Stage 1	Involvement of Nasal mucosa

Materials and methods

Out of 250 Post Covid ROCM cases, randomly 100 patients were selected and a clinical study was undertaken from May 2021 to July 20th 2021. A detailed clinical history waselicited from all the patients including:

- History of positive COVID test and treated for COVID 19
- History of hospital admission and Oxygen therapy
- History, duration and dosage of Steroids either oral or parenteral or inhalational
- History of intake of Zinc supplements
- History of Diabetes and control of blood sugars
- History regarding oral and dental hygiene
- History of Fever, nasal stuffiness, facial pain and numbness, retro-orbital headache, hyposmia, blood-tinged/brownish black nasal discharge
- History of Toothache, loosening of maxillary teeth, jaw involvement
- History of Redness and swelling of eye, diplopia (double vision), visual loss, drooping of eye lid, protrusion of eyeball, black

discoloration on and around lids

- History of altered consciousness

Clinical evaluation is done by a multi-speciality team including an Ophthalmologist, Oto-rhino -laryngologist, Oro-Maxillo-facial surgeon, Physician, Neurologist, Radiologist. Detailed and thorough examination and investigations were performed for each patient. Detailed Ophthalmic examination for Visual acuity, testing Extra ocular movements, Anterior segment examination on Slit Lamp, fundus examination with Indirect Ophthalmoscope.

Following confirmation of the diagnosis, patients were immediately started on therapy depending upon the clinical severity and staging with:

- Tab Posaconazole 300mg twice daily oral or
- Injection Posaconazole 300mg in 300ml DNS IV infusions or
- Injection Liposomal Amphotericin-B IV infusions 5mg/kg in 250 ml D5 IV once daily
- Tab Augmentin 625 mg twice or thrice daily or Injection Monocef 1gm/ Augmentin/Meropenam 1gm IV BD
- Tab Serratiopeptidase 10mg thrice daily
- Injection Tramadol / Tab Diclofenac SOS
- Moxifloxacin 0.5% eyedrops 6 times daily for patients with ocular complaints
- Reconstituted Amphotericin-B eyedrops 10.5mg/10ml 3-4 times daily

Patients with proven fungal etiology on biopsy and culture or on CEMRI with orbital involvement, and with ocular complaints like fall of vision, periorbital edema and discoloration, Proptosis, Ptosis, Ophthalmoplegia/ Diplopia, Conjunctival congestion and discharge, Retro orbital pain:

- 4 doses of Transcutaneous Retrobulbar Amphotericin-B 3.5mg was given for 4 days consecutively. Patients were closely followed for improvement in vision and other ocularcomplaints.
- Depending on improvement or deterioration clinically, the injections are repeated after afollow up of 1 week.
- Later, as there could be a risk of development of Orbital Compartment syndrome, there is shift from consecutive days Retrobulbar injections to alternate days Liposomal Amphotericin-B administration in 4 doses, as a Peribulbar injection into the Peripheral Orbitalspace.
- All the patients are followed for a period of 4 to 6 weeks, detailed Ocular examination isdone and findings are recorded.
- In cases with proven Orbital extension, involving Extra ocular muscles, Retro-orbital fat, extending to base of skull and with Complete loss of vision i.e., Frozen eye- No perception oflight, Proptosis, Ptosis, Chemosis, with complete restriction of all extraocular movements: Orbital Exenteration was performed, if proven orbital extension on MRI.
- In cases with Panophthalmitis – Evisceration or Enucleation was performed (After 4 dosesof TRAMB).
- Orbital lavage was done with reconstituted Amphotericin-B for 1 week post Enucleation.
- For all the Post operative cases IV Liposomal Amphotericin-B 5mg/kg were given.
- Lateral Canthotomy and Cantholysis with Orbital lavage with Amphotericin-B is done forcases with Proptosis.
- At discharge patients were advised Tab Posaconazole 300 mg twice daily for 2 weeks and biweekly follow up. Other symptomatic treatment was also advised along.

Results

All the 100 patients taken in the study had history of being symptomatic and either being tested positive for COVID 19 on RTPCR or Rapid antigen tests or Ground glass opacities on HRCT chest; for which they have undergone treatment for the same. Most of the cases presented with ROCM post recovery from COVID within a time period of 10 days to 2 months

Table 1: Age wise incidence of ROCM among Post COVID patients

Age	Number ofcases
18-30 years	5
31-40 years	10
41-50 years	19
51-60 years	35
>60 years	31

Table showing number of patients with potent Risk factors for development of ROCMamong who recovered from COVID 19 (Table no 2

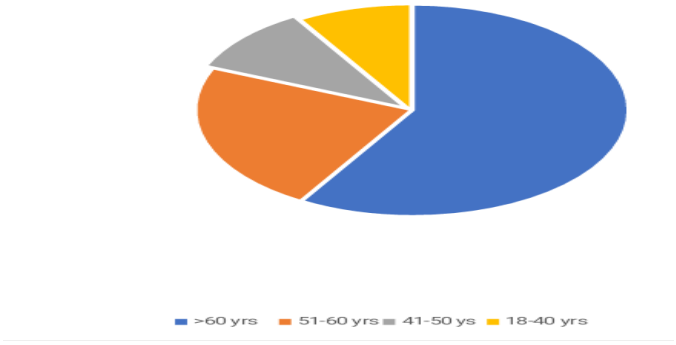

Fig 1:Age wise incidence

Table 2: showing number of patients with potent Risk factors for development of ROCMamong who recovered from COVID 19

Criteria	Number of Patients
Non Invasive Ventilation (CPAP, BIPAP)	9
Non rebreathing mask	17
Hudson mask	22
Nasal prongs	15
Room air	37
History of nasal stuffiness or discharge	71
Diabetics	87
On steroid therapy	78
Use of other immunosuppressive drugs or Immunocompromised individuals	3
Number of patients who underwent home treatment for Covid 19	26
Use of Zinc supplements	87

Out of 100 patients in the study, 89 had uniocular presentation and 11 had binocularpresentation

Table 3: showing incidence of ocular complaints

Ocular presenting features	Number of patients
Periorbital edema and discoloration	94
Ptosis	55
Proptosis	39
Decreased vision or complete loss of vision	35
Diplopia	23
Chemosis	56
Exposure keratitis	18
Ophthalmoplegia	54

For all the 100 patients Transcutaneous Retrobulbar or Peribulbar injection of Liposomal Amphotericin-B 3.5 mg 4 doses for 4 consecutive days or alternate days was given and thefollowing recordings were noted:

- 63 cases (63%) had improvement in symptoms like decrease in edema, pain and no furtherdeterioration of vision, resolution of proptosis and chemosis.
- Of the 63 cases, 40 cases had improvement with 4 doses, and 23 cases required repetition
- of doses after 1 week.
- 18 cases (18%) had neither improvement nor deterioration in ocular complaints.
- 19 cases (19%) were found to have progressive vison loss and orbital involvement, despiteTRAMB.
- Among the 19%, on the basis of CEMRI findings, plan for Exenteration or Evisceration orEnucleation was done.

Clinical photograph no 1

Clinical photograph no 2

- 1 case of Orbital Exenteration along with Maxillectomy was done, for whom CEMRI showedextensive orbital extension.
- Evisceration was done for 3 patients.
- Enucleation was done for 9 patients.
- Lateral Canthotomy and Cantholysis with Orbital lavage was done for 10 patients to resolvethe proptosis and prevent further increase in the orbital compartment pressure, that might lead to CRAO or Compressive Optic Neuropathy.

Above are the photographs of patient at presentation with Proptosis and Ptosis and restriction of ocular movements (Clinical photograph no 1) and after 4 doses of TRAMB(Clinical photograph no 2)

In patients with early diagnosis and administration of TRAMB, vision could be saved and other ocular complaints were resolved. Delay in presentation or diagnosis led to Intracranial extension, landing in poor general condition as well as loss of vision. Initially Retrobulbar administration on consecutive days was done, which later was shifted towards alternate days Peribulbar injections, to prevent the dreaded complication of Orbital Compartment Syndrome, as already due to the invasive fungal infection, there is an increase in the pressure.

Among the 100 cases included in the study, 40 cases had improvement with 4 doses ofTRAMB, 23 cases required repetition of TRAMB after 1 week. Thus 63 cases had improvement in symptoms

with TRAMB. 18 cases had neither improved nor deteriorated[5,6]. even with repetition of the TRAMB after 1 week followup. 19 cases deteriorated despite the injections, for whom destructive ocular surgeries were performed.

Prevention of rocm in covid 19 scenario

- Judicious and supervised use of systemic steroids in compliance with the current preferredpractice guidelines
- Judicious and supervised use of tocilizumab in compliance with the current preferredpractice guidelines
- Aggressive monitoring and control of diabetes mellitus
- Strict aseptic precautions while administering oxygen (sterile water for the humidifier, dailychange of the sterilized humidifier and the tubes)
- Personal and environmental hygiene
- Betadine mouth gargle twice a day (not nasal drops)
- Barrier mask covering the nose and mouth
- Consider prophylactic oral Posaconazole in high-risk patients (>3 weeks of mechanical ventilation, >3 weeks of supplemental oxygen, >3 weeks of systemic steroids, uncontrolled diabetes mellitus with or without ketoacidosis, co-morbidities with immunosuppression)

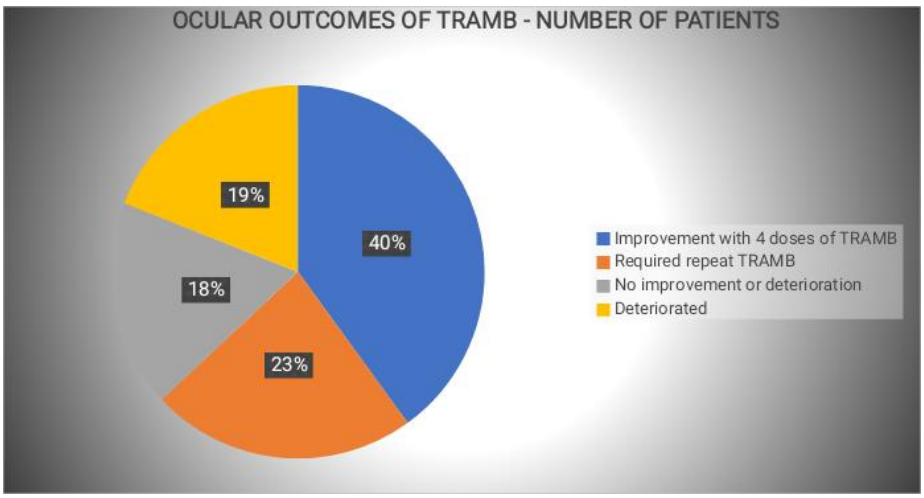

Fig 2: Pie chart showing the Ocular outcomes of TRAMB

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