Outcomes of transcutaneous retrobulbar Amphotericin B (TRAMB) as an adjuvant therapy for rhino-orbital-cerebral mucormycosis (ROCM) following COVID-19

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Abstract
Purpose To assess the outcomes of transcutaneous retrobulbar Amphotericin B (TRAMB) for rhino-orbital-cerebral-mucormycosis (ROCM) post-COVID-19, as an adjuvant to standard systemic antifungal therapy.

Methods In this prospective cohort study involving ROCM patients with clinical/radiological orbital involvement, 44 eyes with ROCM stage ≥ 3B received TRAMB for 7 consecutive days with liposomal Amphotericin-B (3.5 mg/ml) with a minimum clinical and radiological follow-up of 3 months. All patients received standard systemic antifungal therapy also as per institutional protocol. Data pertaining to demography, systemic status, clinical involvement, imaging, surgical/medical management were also recorded. Potential eyes for exenteration were excluded.

Results Forty-four eyes of 42 patients were included, out of which 30 had diabetes mellitus & 22 had received steroid/oxygen treatment during COVID-19 infection. Forty eyes showed improvement or stable disease on follow-up on radiology. Four eyes which showed progression of the disease in orbit were reaugmented with TRAMB. No patient required exenteration. Subconjunctival haemorrhage occurred in six eyes and temporary blurring
of vision in four eyes after TRAMB which resolved spontaneously.

**Conclusion** TRAMB, as an adjuvant to standard systemic antifungal therapy, is associated with a significant reduction or stabilisation of orbital involvement. TRAMB should be considered as an adjuvant therapy for ROCM to reduce disease progression as well as to preserve globe or sight. It has a promising role in preventing potential orbital exenterations.

**Keywords** COVID-19 · Transcutaneous retrobulbar Amphotericin B · Rhino-orbital-cerebral-mucormycosis

**Introduction**

Mucormycosis is a life-threatening fungal infection caused by species of the genus *Mucor* of the order *Mucorales* [1]. It is an opportunistic infection that occurs in immunocompromised individuals leading to severe morbidity and high mortality. Previously rare, the disease entity gained importance as a huge spurt was witnessed during the Coronavirus Disease 2019 (COVID-19) pandemic, with the maximum brunt of the disease being borne by the Indian subcontinent [2]. This unprecedented phenomenon has been attributed to the cellular milieu created by the COVID-19 infection, especially in conjunction with the indiscriminate use of steroid therapy, and co-existing diabetes mellitus (DM) [3]. The interplay of a variety of factors such as hypoxia, acidosis, hyperglycaemia, and immunosuppression, especially in the form of decreased phagocytosis, iron overload, is being held responsible for the sudden outbreak of mucormycosis cases [2]. Other predisposing risk factors, like immunosuppressive drugs, primary or secondary immunodeficiency, haematological malignancies/haematological stem cell transplantation, solid organ malignancies/solid organ transplantation, have been previously described [4]. The angioinvasive fungal infection results in ischaemia and necrosis of the tissue involved. It has been diagnosed as possible, probable, and proven cases and staged on the basis of anatomical involvement [5]. A sudden surge of rhino-orbital-cerebral-mucormycosis (ROCM) has been reported in patients with COVID-19 [3]. The infection first lodges in the sinuses and may spread contiguously to the orbit and central nervous system (CNS). It is rapidly progressive in the absence of treatment and has a high mortality rate [6]. Due to high volume of mucormycosis, it has already been declared as an epidemic in several parts of India.

The standard treatment includes debridement of necrotic tissue and systemic antifungal therapy [7]. Exenteration is indicated for eyes with extensive orbital involvement including apex with no light perception or in disfigured blind eye with central retinal artery occlusion (CRAO), or in eyes with some vision but disease progression even after sinus debridement with antifungal therapy [8]. The treatment modalities in cases of orbital involvement are limited. However, exenteration is not a viable option in eyes with useful vision or limited orbital involvement and causes extensive disfigurement. In such cases, transcutaneous retrobulbar Amphotericin B (TRAMB) can be a useful alternative. It is a short, minimally invasive, globe saving office procedure obviating the need for general anaesthesia. It has been shown to successfully treat a case of orbital mucormycosis [9]. The data related to use of TRAMB in ROCM are limited. In this study, we have explored the promising role of TRAMB as an adjuvant therapy in minimising morbidity and preventing orbital exenteration in ROCM.

**Material and methods**

A prospective study of ROCM patients with orbital involvement treated at our hospital from April 2021 to July 2021 was done. Institutional ethical clearance was obtained (AIIMS/IEC/2021/3553) and this study adheres to the tenets of Declaration of Helsinki. A written informed consent was taken from all patients. The diagnosis of ROCM was based on KOH mount, histopathology and radiology (Contrast enhanced CT and/or MRI of brain, paranasal sinuses and neck). The staging for all ROCM cases was done as proposed by Honavar et al. [5]. All ROCM patients with stage ≥ 3B with clinical and/or radiological orbital involvement were included in this study. Stage 3B included patients with diffuse orbital involvement with >1 quadrant or >2 structures with vision unaffected. Patients with ROCM stage 1-3A, potential eyes for exenteration, which included disfigured eyes with nil visual potential or with CRAO were excluded from the study. Patients with low platelet counts who had risk of retrobulbar haemorrhage after
TRAMB were also excluded from the study. History of COVID-19 was ascertained by medical records or RT-PCR/Antigen testing. A detailed history including demographic details, systemic status like DM/hypertension, any previous treatment taken at the time of COVID-19 in the form of systemic steroids/supplemental oxygen therapy/mechanical ventilation/medications, was documented. The clinical involvement of orbit was confirmed by contrast enhanced MRI and/or CT. Blood investigations were sent for all patients. A detailed eye examination consisted of best corrected visual acuity (BCVA), eyelids & conjunctival examination, pupillary reaction, extraocular movements, anterior segment and posterior segment evaluation was documented in a standardised format. Details of medical and surgical treatment received were also noted. Patients with ROCM staging ≥ 3B received TRAMB for 7 consecutive days with liposomal Amphotericin-B with a strict clinical and radiological follow-up for a minimum of three months. All patients received Inj. Amphotericin B ± Tab. Posaconazole as per Institutional protocol which included injection liposomal Amphotericin B 5 mg/kg of body weight for 3–6 weeks ± Tab Posaconazole 300 mg BD on day one followed by 300 mg OD for 3–6 months.

Patients who were receiving low molecular weight heparin or any other anticoagulants were administered TRAMB 5 days after withholding heparin/anticoagulants [10]. Liposomal Amphotericin B was reconstituted with sterile water in a concentration of 3.5 mg/ml. TRAMB was administered daily for 7 consecutive days. Any TRAMB-related side-effects were documented. TRAMB was withheld in case of any acute inflammatory reaction till its resolution. TRAMB was reaugmented for 7 consecutive days if disease progression was noted radiologically after a month.

Patient was laid supine in a comfortable position with head supported. Periocular area was cleaned with 10% betadine solution under all aseptic precautions. The patient was asked to look straight in upper direction. One millilitre of 2% lignocaine was injected first, followed by 1 ml of 3.5 mg/ml Amphotericin B with 23-gauge 24-mm needle. After palpating the inferior orbital rim, 23-gauge needle was inserted at the junction of lateral 1/3rd and medial 2/3rd with bevel up in posterior and inferior direction along the floor of the orbit for at least 15 mm. The direction of the needle was then changed superomedially, and a resistance was felt as the needle passed through the muscle cone. 2% Lignocaine was injected slowly, followed by Amphotericin B immediately. Eyelid closure with an eye pad, along with gentle globe pressure was applied for at least 7–10 min. Eye pad was removed after 4 h.

Eye examination was done twice daily till two weeks from 1st TRAMB injection administration. A repeat imaging was done after one week of last TRAMB for comparison. Thereafter, all patients were followed up one weekly and repeat imaging was done every 4 weekly.

All the data were entered in a Microsoft excel sheet. The paired t test was used to analyse quantitative data. Chi-square and Fisher’s exact tests were used to analyse categorical data. Statistical analysis was performed using SPSS software (College station, Texas, USA). A p-value of < 0.05 was considered statistically significant.

Results

Forty-four eyes with stage ≥ 3B disease were included in the study. All patients had received intravenous Amphotericin B as the primary treatment modality. Intravenous Amphotericin B was contraindicated in two patients; therefore, they received TRAMB along with oral posaconazole. All patients underwent stage appropriate surgical debridement (endoscopic endonasal debridement/partial/total/radical/extended radical maxillectomy). Two patients in group 1 had bilateral involvement who had received TRAMB in both the eyes but on different sittings.

The mean age of patients was 52.50 ± 8.14 years with a male/female ratio of 2.1:1. COVID-19 test was positive in 20 patients at the time of admission. Type 2 DM was seen in 71.42% (30/42) patients with a mean HbA1c of 12.56%. A majority (52.38%, 22/42) of patients had a history of oxygen supplementation at the time of COVID-19 infection, with 17 of these requiring ventilator support. Steroid use was ascertained in 50.0% (21/42) patients (Table 1).

84.09% (37/44) eyes had visual acuity of ≥ 6/60. Subnormal vision in four eyes was due to cataract. Complete ophthalmoplegia was noted in two eyes whereas some limitation of extraocular movements was noted in thirteen eyes. Ptosis, propotis or chemosis was seen in nineteen eyes (Table 2).
On first radiological follow-up, four weeks after the last TRAMB administration, we found that 52.27% (23/44) eyes improved, 38.63% (17/44) were stable, and 9.09% (4/44) showed progression of disease (Fig. 1). Four eyes which showed progression of the disease in orbit were reaugmented for 7 more days and were found to have stable orbital disease on subsequent radiological follow-up. Improvement in visual acuity was seen in 3 eyes, while complete resolution of extraocular movement limitation was seen in thirteen eyes after 3 months (Fig. 2). Exenteration was not required in any eye. Multiple debridement was required in 76.19% (32/42) patients within 2 months. Five patients were deceased during the course of the disease due to systemic causes. The rest of the patients are still under follow-up (Table 3).

Total or partial subconjunctival haemorrhage and chemosis occurred in six eyes after TRAMB which resolved completely without any intervention within a week. Blurring of vision was noted in four eyes after TRAMB, which recovered within a week. Injection was withheld in that duration. Complete restriction of movements along with periorbital oedema, ptosis, chemosis occurred in one patient after 3 doses of TRAMB, which also resolved completely within

| Characteristics                        | n = 44 eyes of 42 patients |
|----------------------------------------|----------------------------|
| Age (years)                            | 52.50 ± 8.14               |
| Gender (male/female)                   | 2.1:1                      |
| RT-PCR COVID-19 test positive          | 20                         |
| Diabetes mellitus                      | 30                         |
| Oxygen treatment given during COVID-19 | 22                         |
| Steroid treatment given during COVID-19 infection | 21                     |
| HbA1c (mean)                           | 12.56%                     |
| D-Dimer (mean)                         | 2.17 ug/ml                 |
| Serum ferritin (mean)                  | 834 ng/ml                  |
| ROCM staging                           |                            |
| 3A                                     | 0                          |
| 3B                                     | 22                         |
| 3C                                     | 12                         |
| 3D                                     | 2                          |
| 4A                                     | 3                          |
| 4B                                     | 2                          |
| 4C                                     | 1                          |
| 4D                                     | 0                          |

**HbA1c** Glycated haemoglobin, **ROCM** Rhino-orbital-cerebral-mucormycosis,

**ROCM staging** 3A—Nasolacrimal duct, medial orbit, vision unaffected, 3B—Diffuse orbital involvement (>1 quadrant), vision unaffected, 3C—central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis; involvement of superior/inferior orbital fissure, orbital apex, loss of vision, 3D—bilateral orbital involvement, 4A—Focal or partial cavernous sinus or cribriform plate involvement, 4B—diffuse cavernous sinus involvement or thrombosis, 4C—involvement beyond cavernous sinus, skull base, internal carotid artery occlusion, brain infarction, 4D—multifocal or diffuse CNS disease

| Table 2 Ocular signs on presentation                           | n = 44 eyes |
|---------------------------------------------------------------|-------------|
| Visual acuity                                                 |             |
| < 6/60                                                        | 7           |
| 6/60-6/18                                                     | 2           |
| 6/12-6/6                                                      | 35          |
| Ptosis                                                        | 8           |
| Proptosis                                                     | 6           |
| Chemosis                                                      | 5           |
| Fixed non-reacting Pupillary reaction                         | 9           |
| Limitation of extraocular movements                           | 15          |

**Fig. 1** Pre- and post-CT after TRAMB. 1a—CT orbit (axial section) showing soft tissue extension through inferomedial region of left orbit involving medial and inferior rectus, intraconal extension abutting the orbital part of left optic nerve up to orbital apex on left side (red arrow). 1b—CT orbit showing resolution of the disease (green arrow)
19 days and the treatment course was completed thereafter (Fig. 3).

**Discussion**

An upsurge of ROCM after second wave of COVID-19 from April 2021 has occurred, during which we had also reported clinical profile of few cases of ROCM presenting to us [11]. In the present study, the authors reported the baseline demographic/clinical profile of post-COVID-19 ROCM and treatment outcomes of adjuvant TRAMB in orbital involvement.

Uncontrolled old or new onset DM and history of steroid use were found to be unfavourable factors for Coronavirus disease-associated mucormycosis (CAM) [2, 12–14]. We had 71.42% diabetic patients. Majority of our patients had history of oxygen supplementation or steroid use at the time of COVID-19 infection suggesting both as an important risk factors for ROCM.

Surgical debridement and intravenous Amphotericin B are endorsed treatment option for managing ROCM [3, 5]. Damage to endothelial cells and vessel thrombosis reduces the amount of drug delivered to the desired site and eventually decreases the efficacy of systemic treatment. Orbital exenteration which causes a significant disfigurement is one of the surgical options for patients with orbital involvement which is mostly reserved for disfigured blind eyes with no light perception/CRAO/not responding to intravenous antifungals, diffuse involvement of the orbital apex with no visual potential [8]. Exenteration should be avoided in eyes with extensive involvement on imaging but with any visual potential and any improvement noted after sinus debridement surgery. Limited orbital debridement along with local irrigation with antifungals is another option [15]. TRAMB is a good alternative for the eyes with preserved vision and focal involvement of the orbit, unavailability or contraindication for intravenous Amphotericin B, or eyes in which orbital wall has been breached after sinus debridement [8]. We also included the eyes with more than 1 orbital quadrant (stage ≥ 3B) involved with any amount of preserved vision, patients with contraindication to intravenous Amphotericin B, or any breach in the inferior orbital wall after sinus debridement for TRAMB. 84.09% eyes in our study had visual acuity of > 6/60. Use of retrobulbar antifungal injections for orbital fungal related infections has been reported prior to COVID era too [9, 16–19]. The number of injections and optimal dose to be given for ROCM is still unclear. Turbin et al. used 3–5 ml of 2 mg/ml Amphotericin B for retrobulbar injection in invasive sino-orbital fungal infection [16], whereas 1 ml of 3.5 mg/ml for retrobulbar injection for ROCM for up to 6 days was also reported by authors in the past [6, 14]. We used 1 ml of 3.5 mg/ml Amphotericin B for seven consecutive days for our patients. Till now, we have limited literature on TRAMB for ROCM management associated with COVID-19 [17].
Ptosis, chemosis, proptosis, limitation of extraocular movements, fixed/non-reacting pupils and reduction in vision were the common presentations of our patients as described in previous studies too [14, 16, 17]. Orbital cellulitis was not a presenting feature in any of our patients, though it has been reported as the most common presentation by Soumya et al. [19]. A significant number of eyes were either improved or stable (90.90%) on repeat imaging, while improvement in visual acuity was seen in 6.81% eyes. Halt in disease progression along with restoration of visual acuity in ROCM was also reported by Hirabayashi et al. [9]. Pandian et al. reported a case of orbital apex syndrome secondary to mucormycosis after COVID-19, who received retrobulbar liposomal Amphotericin B at the time of redebridement surgery (craniotomy with medial orbitotomy) for further worsening of eye signs. They found a full recovery in visual acuity along with partial recovery in EOM at 6 weeks [20]. Turbin et al. also reported improvement in vision in two patients and improvement in motility in five patients in invasive sino-orbital fungal infections after retrobulbar injection of Amphotericin B along with sino-orbital irrigation [16]. Resolution of extraocular movement limitation was also found in 86.67% eyes after TRAMB in our study. Previous studies had used retrobulbar Amphotericin B after progression of orbital disease or worsening of clinical signs [16, 20]. We had given TRAMB to all patients who presented to us with orbital involvement on first presentation itself.

Orbital exenteration was not required in any patient in the study done by Turbin et al. [16]. In our study also, none of the eyes underwent orbital exenteration after TRAMB. Safi et al. documented a case of ROCM with focal cerebritis with no improvement after intravenous antifungal therapy and endoscopic debridement [17]. They administered two doses of retrobulbar deoxycholate Amphotericin B three days apart and found a significant improvement in orbital progression along with resolution of cerebritis. They suggested retrobulbar Amphotericin B should be considered in presence of evidence of progression on systemic treatment in a seeing eye and cerebritis. We had repeated TRAMB in four eyes which showed progression on first follow-up and found that the disease had stabilised after reaugmentation. Therefore, we suggest TRAMB should be considered in the presence of orbital involvement with whatever preserved vision. We also recommend that early intervention in the form of TRAMB should be considered if more than one orbital compartment is involved rather than waiting till diffuse orbital involvement occurs.

Fig. 3 Post-TRAMB complication. 3a–c Periorbital oedema, ptosis, chemosis with total ophthalmoplegia in left eye after 3 TRAMB injections. 3d–f Complete resolution after 5 days.
An inflammatory response in the form of conjunctival chemosis, proptosis or orbital compartment syndrome after retrobulbar injection has been reported which resolves in about a week [9, 17]. We also found total or partial subconjunctival haemorrhage/chemosis, transient drop in visual acuity, as well as total ophthalmaloplegia with subconjunctival haemorrhage/chemosis in one patient which resolved spontaneously, not reported so far. Orbital compartment syndrome was not seen in any patient.

ROCM requires a multidisciplinary approach of management. TRAMB is helpful in halting orbital progression, sparing residual vision and for globe salvage. It should be considered for ROCM in seeing progression, sparing residual vision and for globe management. TRAMB is helpful in halting orbital chemosis in one patient which resolved spontaneously. However, studies with long-term follow-up are definitely required to establish a definitive approach.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jyoti Shakrawal, and Vidhu Sharma. The first draft of the manuscript was written by Kavita R Bhatnagar, Jyoti Shakrawal, Vidhu Sharma and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of AIIMS Jodhpur. (AIIMS/IEC/2021/3553).

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Sugar AM (1992) Mucormycosis. Clin Infect Dis 14:S126–S129
2. Singh AK, Singh R, Joshi SR, Misra A (2021) Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 15:102146
3. Aranjani JM, Manuel A, Abdul Razack HI, Mathew ST (2021) COVID-19–associated mucormycosis: evidence-based critical review of an emerging infection burden during the pandemic’s second wave in India. PLoS Negl Trop Dis 15:e0009921
4. Skaida A, Pavleas I, Drogari-Apiranthitou M (2020) Epidemiology and diagnosis of mucormycosis: an update. J Fungi (Basel, Switzerland) 6:E265
5. Honavar SG (2021) Code mucor: guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. Indian J Ophthalmol 69:1361–1365
6. Cornely OA, Alastruey-Izquierdo A, Arentz D, Chen SCA, Dannaoui E, Hochhegger B et al (2019) Global guideline for the diagnosis and management of mucormycosis: an initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet Infect Dis 19:e405–e421
7. Kalin-Hajdu E, Hirabayashi KE, Vagefi MR, Kersten RC (2017) Invasive fungal sinusitis: treatment of the orbit. Curr Opin Ophthalmol 28:522–533
8. Naik M (2021) Transcutaneous retrobulbar Amphotericin B and exenteration in rhino-orbital cerebral mucor mycosis: Do we know it all yet? TNOA J Ophthalmic Sci Res 59:131
9. Hirabayashi KE, Kalin-Hajdu E, Brodie FL, Kersten RC, Russell MS, Vagefi MR (2017) Retrobulbar injection of Amphotericin B for orbital mucormycosis. Ophthalm Plast Reconstr Surg 33:e94–e97
10. Benzimra JD, Johnston RL, Jaycock P, Galloway PH, Lambert G, Chung AKK et al (2009) The cataract national dataset electronic multicentre audit of 55,567 operations: antiplatelet and anticoagulant medications. Eye (Lond) 23:10–16
11. Shakrawal J, Bhatnagar KR, Roy F (2021) Epidemic in pandemic: a battle in the war. Indian J Ophthalmol 69:1971–1972
12. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhatta A et al (2021) Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. Mycopathologia 186:289–298
13. Kashkouli MB, Abdolalizadeh P, Oghazian M, Hadi Y, Karimi N, Ghazizadeh M (2019) Outcomes and factors affecting them in patients with rhino-orbito-cerebral mucormycosis. Br J Ophthalmol 103:1460–1465
14. Dave TV, Gopinathan Nair A, Hegde R, Vithalani N, Desai S, Adulkar N et al (2021) Clinical presentations, management and outcomes of rhino-orbital-cerebral mucormycosis (ROCM) following COVID-19: a multicentric study. Ophthalmic Plast Reconstr Surg 37:488–495
15. Joos ZP, Patel BCK (2017) Intraorbital irrigation of Amphotericin B in the treatment of rhino-orbital mucormycosis. Ophthalm Plast Reconstr Surg 33:e13–e16
16. Turbin RE, Khoobiar SA, Langer P, Amusur K, Frohman L, Warren F et al (2002) Adjuvant therapy for invasive sino—orbital fungal infection. Invest Ophthalmol Vis Sci 43:2637
17. Safi M, Ang MJ, Patel P, Silkiss RZ (2020) Rhino-orbital-cerebral mucormycosis (ROCM) and associated cerebritis treated with adjuvant retrobulbar Amphotericin B. Am J Ophthalmol Case Reps 19:100771
18. Colon-Acevedo B, Kumar J, Richard MJ, Woodward JA (2015) The role of adjunctive therapies in the management of invasive sino-orbital infection. Ophthal Plast Reconstr Surg 31:401–405

19. Soumya MS, Menezes V, Sreenivas VV, Balasubramanya AM (2014) Institutional experience of mucormycosis over a period of 10 years—retrospective case series. Int J Adv Med 1:1

20. Pandian E, Kang J, Mph MD, Cockerham K (2021) The role of retrobulbar liposomal amphotericin in orbital apex syndrome in a COVID-19 positive diabetic journal of medical clinical case reports case report. J Med Case 3:2021

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