



Retrobulbar Amphotericin B Injection in Curbing the Progression of COVID Associated Rhino-orbital Cerebral Mucormycosis: A Retrospective Case Series

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Abstract *Purpose* To assess whether transcutaneous retrobulbar Amphotericin B (TRAMB) injection can halt disease progression and reduce the requirement of exenteration in post-COVID 19 Rhino-orbital cerebral Mucormycosis (ROCM) with limited orbital disease. *Methods* Retrospective series from a single center included 22 patients with KOH proved post-COVID 19 ROCM with radiographic evidence of limited orbital involvement were evaluated from May 2021 to October 2021. TRAMB was given along with systemic intravenous Amphotericin B injection and sinus debridement. Demographic profile, clinical data, operative notes, blood and radiological investigations were evaluated. The primary outcome was to assess the halt in the progression of orbital disease. The primary outcome measure was to assess the halt of the disease progression and the secondary outcome was improvement in the clinical signs and symptoms. *Results* The mean age was 50.36 ± 9.72 years and 77.3% were men. The Stagemwise distribution was twelve (54.5%) patients in stage 3a, four (18.2%) patients in stage 3b, four (18.2%) in stage 3c, one (4.5%) patient in stage 3d and one (4.5%) had stage 4 disease. Improvement in lid edema and conjunctival chemosis were noticed and it was statistically significant (p value < 0.01), similarly visual acuity and ocular motility showed significant improvements (p value 0.04 and < 0.01 respectively). 1 patient died and 1 patient required exenteration later. Twenty patients showed

halting of orbital disease after TRAMB injection. *Conclusion* TRAMB can be an alternative adjuvant therapeutic option to preserve the globe in patients with limited orbital disease but not at all replacement for exenteration.

Keywords Rhino-orbital-cerebral Mucormycosis · retrobulbar injection · exenteration · sinus debridement

Introduction

Mucormycosis is an aggressive fungal infection associated with high morbidity as well as mortality. The causative agent belongs to order Mucorales of the class Zygomycetes, which are ubiquitous in nature and includes Rhizopus, Mucor, Rhizomucor, Lichtheimia, Cunninghamella, and Apophysomyces [1–3].

Rhizopus and mucor are the most common genus causing Mucormycosis. After inhalation through the nose or oral cavity, the fungal spores get access to the paranasal sinuses and then to the orbit via the thin lamina papyracea of the ethmoid bone, infratemporal fossa, inferior orbital fissure, or orbital apex. The intracranial extension can occur via the cribriform plate of the ethmoid, supraorbital fissure, or perineural invasion [4, 5]. The most susceptible ones for infection are the immunocompromised patients. Recently, the COVID 19 pandemic created a situation responsible for the Mucormycosis outbreak. The immune dysregulation seen in COVID-19 patients is characterized by decreased T cells, including CD4 and CD8 cells, altering the innate immunity [6]. Hence the opportunistic fungal infections were on the rise at the time of COVID-19 infections or dur-

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ing the recovery. One such fatal opportunistic infection was COVID-associated Mucormycosis (CAM). According to sources in the Union health ministry, there were more than 45000 cases and over 2,000 deaths by Mucormycosis till July 2021, which had increased to 51,775 cases by the end of November 2021 [7]. CAM can be classified based on site of infection as pulmonary, cutaneous, gastrointestinal, disseminated, and rhino-orbital-cerebral Mucormycosis (ROCM) [8]. ROCM is the most common clinical manifestation of Mucormycosis and is implicated to be fatal, vision-threatening, rapidly progressive, angioinvasive infection. A multifaceted approach is necessary in managing Mucormycosis cases that include systemic antifungal agents, surgical debridement, and/or orbital exenteration, along with the treatment of the underlying predisposing clinical condition [9, 10]. Early diagnosis and treatment play a vital role in ROCM cases for reducing morbidity and mortality. Although the surgical debridement of the sinuses and/or exenteration is the mainstay in the management of ROCM, in advanced orbital disease, and in patients who show disease despite medical and surgical treatments, exenteration stood as the last resort [11]. So, Orbital exenteration may be asserted in advanced orbital involvement with total vision loss and the frozen globe; however, in selected cases of limited orbital involvement with some preserved vision, exenteration may be an arduous decision for the surgeon as such patients may not comfortably consent for such destructive procedure. Exenteration causes disfigurement and increases the morbidity of the patients, and many authors reported it does not affect patients' survival [12]. Unfortunately, there is no standard guideline for the management of the limited orbital disease. So, there is a dearth of a viable option for the management of the orbital component of ROCM, especially in limited diseases. Retrobulbar Amphotericin B injection may be considered a globe-sparing technique. It can be given as an adjuvant therapy along with the conventional management to salvage the affected eye in some selected cases [13]. There have been few case reports about the use of retrobulbar Amphotericin B injection in orbital Mucormycosis described by various authors from different corners of the world [14–20]. We report a retrospective case series of 22 patients (22 eyes) injected with TRAMB for post-COVID 19 ROCM in a Tertiary Care Centre in Chhattisgarh, India. We have analysed the effects of TRAMB retrospectively in terms of prevention of disease progression and trying to establish it as a viable globe-sparing technique.

Materials and Methods

A retrospective case series was carried out that included 22 eyes of 22 patients of post COVID-19 ROCM who were admitted to All India Institute of Medical Sciences Raipur, Chhattisgarh, India, and injected with TRAMB from May 2021 to October 2021. Written informed consent was obtained from all the patients. We carried out the study as per the tenets of the Declaration of Helsinki. Case files from the medical record department (MRD) were identified, and demographic data, clinical history, clinical findings, blood, and radiological investigations, along with operative notes, were extracted. Information about the immunosuppressive status of the patients, if any, was also looked for.

The inclusion criteria for retrobulbar injection of Amphotericin B were found to be all ROCM patients who were KOH positive with limited orbital involvement with preserved vision or patients with poor vision, but radiological evidence suggestive of limited orbital disease, mainly stage 3a and stage 3b. Patients showing fat stranding in more than two quadrants in MRI orbit and no muscle enhancement in contrast MRI orbit were excluded for the injection. Few patients (stage 3c, stage 3d) with advanced disease were also selected, the reason being, probably to see the efficacy of the injection and the disease itself, which is new for the whole fraternity; hence the criteria of patient selection was also less known. A complete ophthalmological workup was done for all the patients selected for retrobulbar Amphotericin B injection, including visual acuity, thorough slit-lamp examination, fundus examination by indirect ophthalmoscope, and extraocular movements. Initial visual acuity was measured with a standard Snellen chart and finally converted to the logarithm of the minimum angle of resolution (log MAR) for the purposes of statistical analysis. Ocular movements were examined in the horizontal (abduction and adduction) and vertical gazes (superior and inferior), and each direction of gaze rated on a scale from 0 (full movement) to -4 (no movement). An average of the four directions of gaze was used for statistical analysis. MRI (contrast) orbit, brain, and paranasal sinuses were advised for all the patients before injection.

The staging of all the patients was done according to the clinical signs and radiological involvement of orbit, following the guidelines of Code Mucor: Guidelines for the Diagnosis, Staging, and Management of Rhino-Orbital-Cerebral Mucormycosis in the Setting of COVID-19 proposed by Honavar SG [21]. Those with involvement of the nasal mucosa were classified as stage 1 (subclassified as 1a-disease limited to middle turbinate, 1b-involvement of the inferior turbinate or ostium of the nasolacrimal duct, 1c-nasal septum involvement, 1d- bilateral nasal septum involvement), those with involvement of the paranasal sinuses were stage 2 (subclassified as 2a- one sinus involvement, 2b- two ipsilateral sinus involvement, 2c-more than 2 ipsilateral sinus and/

or oral cavity/palate involvement), orbital involvement was stage 3, (further classified in 3a-vision unaffected, nasolacrimal duct and medial orbit involved, 3b-vision unaffected with more than one quadrant or more than two structures involvement, 3c-loss of vision, central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis, superior orbital fissure, inferior orbital fissure or orbital apex involvement, 3d- involvement of bilateral orbit) and intracranial involvement was classified as stage 4(4a-focal or partial cavernous sinus involvement and/or involvement of cribriform plate, 4b-diffuse cavernous sinus involvement, 4c- involvement beyond cavernous sinus, base of the base of the skull, occlusion of internal carotid artery and brain infarction, 4d- diffuse CNS disease). The primary management of all cases involved sinus debridement by an endoscopic approach or combined (open and endoscopic) approach and administration of intravenous Amphotericin B injections (lyophilized, conventional, and Amphotericin B lipid complex). After proper patient selection, TRAMB injections were started before or after sinus debridement. A total of 5 doses of TRAMB injections were given on alternate days at the bedside [Figure 1]. The Liposomal Amphotericin B injection was first reconstituted with 14ml distilled water to get the concentration of 3.5mg/ml. The eye to be injected was first instilled with topical proparacaine 0.5% followed by painting of the periocular skin using sterile gauze soaked in 10% povidone-iodine, starting from the eyelids and moving outward in circular motion. All patients were administered local anesthesia with a retrobulbar injection of 1 mL of lidocaine.

23gauge needle. After five minutes, using a 23-gauge needle, 1 mL of the drug was delivered into the retrobulbar

space and gentle pressure was applied over the eyes after the injection. The area of injection was decided based on radiological findings. All the risks involved following retrobulbar injection were explained to the patients. Post injections until 72 h, any serious adverse effects were closely examined. A repeat MRI orbit (contrast) was advised in all the patients within a span of one month. The primary outcome measure was to assess the halt of the disease progression, confirmed by radiologically and the secondary outcome was to look for any improvement in the clinical signs and symptoms like pain, chemosis, ptosis, proptosis, and restricted ocular movements.

Statistical Analysis

The data collected were tabulated in an excel sheet, and the means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). The difference between the two groups was determined using the chi-square test, and the level of significance was set at $p < 0.05$.

Results

A total of 22 eyes of 22 patients were included for the TRAMB. Of these, 17(77.3%) of the patients were male, and 5(22.7%) were female. The mean age was 50.36 +/- 9.72 years. All the patients were either known cases of diabetes or recently had high blood sugar levels following COVID infection. Table 1 shows demographic and clinical data

Fig. 1 Figure showing bedside administration of transcutaneous retrobulbar liposomal amphotericin B injection



Table 1 Demographic profile and clinical characteristics of patients with rhino-orbito-cerebral mucormycosis

Variable	Value
<i>Gender (n = 22)</i>	
Male	17 (77.3%)
Female	5 (22.7%)
<i>Age Group (in years) (n = 22)</i>	
31–40	4 (18.18%)
41–50	6 (27.27%)
51–60	9 (40.91%)
> 60	3 (13.64%)
<i>Ocular signs (n = 22)</i>	
Ptosis	16 (72.7%)
Proptosis	14 (63.6%)
Lagophthalmos	3 (13.6%)
Lid Edema	9 (40.9%)
Conjunctival chemosis	13 (59.1%)
Orbital apex syndrome	6 (27.3%)
Central retinal artery occlusion	5 (22.7%)
<i>Presenting visual acuity (n = 22)</i>	
> 6/9	0 (0%)
6/18 – 6/12	5 (22.7%)
6/60 – 6/36	5 (22.7%)
5/60 – 1/60	6 (27.3%)
Light perception	3 (13.6%)
No light perception	3 (13.6%)
<i>Rhino -orbito-cerebral mucormycosis Staging (n = 22)</i>	
Stage 3a	12 (54.5%)
Stage 3b	4 (18.2%)
Stage 3c	4 (18.2%)
Stage 3d	1 (4.5%)
Stage 4	1 (4.5%)

and staging of ROCM. Table 2 compares various ocular manifestations before and after the injection. Table 3 compares visual acuity and ocular movements before and after injection. After the completion of 5 doses of TRAMB, we

Table 2 Ophthalmic examination data of patients with rhino-orbital-cerebral mucormycosis (pre and post injection)

Variable	Pre-Injection	Post-Injection	p value
Ptosis	16 (72.7%)	16 (72.7%)	1
Proptosis	14 (63.6%)	12 (54.5%)	0.57
Lagophthalmos	3 (13.6%)	3 (13.6%)	1
Lid edema	9 (40.9%)	0 (0.0%)	0.001*
Conjunctival chemosis	13 (59.1%)	0 (0.0%)	<0.01*
Orbital apex syndrome	6 (27.3%)	6 (27.3%)	1
Central retinal artery occlusion	5 (22.7%)	5 (22.7%)	1

Table 3 Comparison of vision and ocular movements (pre and post injection)

Variable	Pre-injection		Post-injection		p value
	Mean	SD	Mean	SD	
Vision	2.14	1.14	2.25	1.25	0.039*
Ocular movement	- 2.05	- 0.89	1.27	1.41	< 0.01*

observed that visual acuity was maintained or improved in the majority of patients, which was statistically significant. However, in patients with no perception of light, visual acuity did not improve, and such one patient later required exenteration. Of all the clinical presentations, some improvement was observed in lid edema and conjunctival chemosis after completing the five doses of TRAMB. Nine eyes showed resolution of lid edema post-injection, and 13 eyes showed resolution of conjunctival chemosis, and improvement of these two parameters (lid edema and conjunctival chemosis) were statistically significant. There was a slight improvement in proptosis but was not statistically significant. Other clinical signs like ptosis, lagophthalmos, Orbital Apex Syndrome, and Central retinal artery occlusion did not improve. However, the ocular movements showed statistically significant improvement post-injection (Figs. 2, 3) [Table 3]. MRI orbit(contrast) did one-month post-injection showed no progression of the disease; in fact, in a few patients, there was some resolution (Fig. 4). The TRAMB injections were given with an aim to halt the progression of the disease, thereby salvaging the globe. The progression of the disease was significantly controlled in stage 3a,3b, and 3c patients, i.e., the condition did not deteriorate following TRAMB as evident from the MRI orbit pre and post injections. One patient in Stage 3d had to undergo orbital exenteration despite TRAMB, and one patient died who had intracranial extension at the time of presentation (Stage 4). The effects of the TRAMB seen in the patients can be said as an additive effect along with the intravenous liposomal Amphotericin B. None of the patients reported any serious adverse effects following the injections like orbital compartment syndrome; only five patients showed yellow tint inferior chemosis and congestion in four patients, which resolved after four-five days.

Discussion

The authors presented the effect of TRAMB in post-COVID ROCM from a single tertiary care centre. ROCM is a potentially fatal sight-threatening infection due to ischemic necrosis of the tissue with angioinvasion, and arterial perfusion and venous return within orbit get grossly diminished. Due to this, antifungal medications given systemically may not reach the diseased site in the required concentration. So,

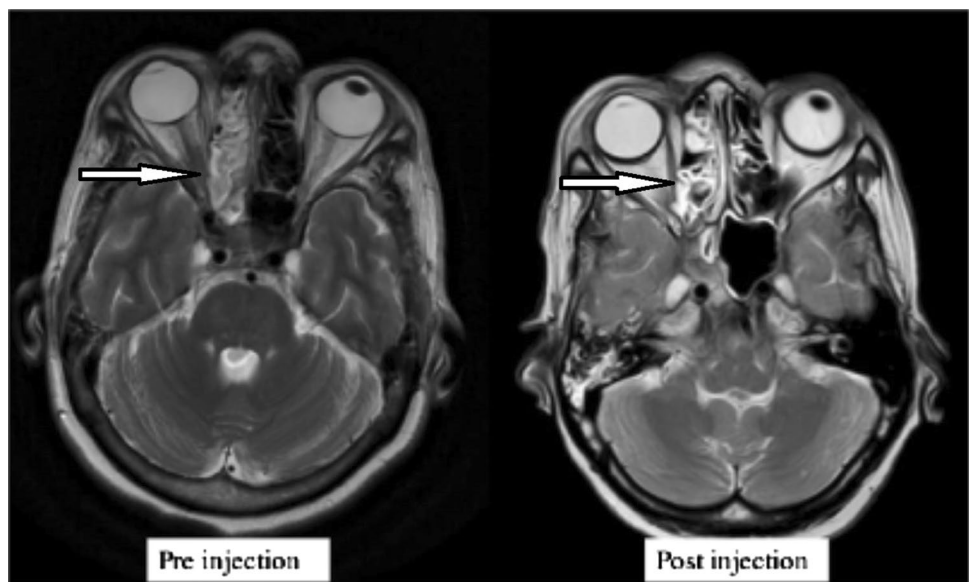


Fig. 2 figure (pre injection) showing restricted ocular motility, figure (post injection) showing improved ocular motility



Fig. 3 figure showing restricted ocular motility pre injection, figure post injection showing improved ocular motility

Fig. 4 T2 axial scan reveal heterogeneously hyperintense signal near completely opacifying right ethmoidal sinus with mild focal extension into the right orbit in posteromedial aspect in retro-orbital extraconal location (pre retrobulbar injection) and no significant increase in lesion size seen post retrobulbar injection



local injection of antifungal drugs may be more beneficial in such cases [1]. In this case series, we retrospectively studied 22 patients (22 eyes) who received TRAMB. The decision to consider a diagnosed case of ROCM for retrobulbar Amphotericin B injection is crucial. The selection of the patients for TRAMB, as seen from the medical records in this case series, was based on radiological evidence on the contrast MRI orbit. Kalin-Hajdu et al., and Ashraf et al. also selected patients for TRAMB in a similar fashion [16, 17]. In their review article on TRAMB, Nair et al. have highlighted that the proper selection of patients for the retrobulbar injections plays a crucial role in achieving the favourable outcome [22]. In our Institute liposomal Amphotericin B(L-AMB) for TRAMB was used, similar to Ashraf et al, Bayram et al., Mekonnen et al., and., in contrast to Hirabayashi et al. and Safi et al., who used Amphotericin B deoxycholate for the TRAMB in their reported cases [17–19, 15, 14]. Although, a comparison between L-AMB and Amphotericin B deoxycholate has not been done yet. Ashraf et al. used 3.5mg/ml of L-AMB in their study, followed by our Institute [17]. Safi et al. and Hirabayashi et al also injected the same concentration but was of Amphotericin B deoxycholate [14, 15].

In the present study, all patients received a total of five injections, a few before and a few after the surgical debridement, similar to Hirabayashi et al., who also gave few injections before sinus debridement and few after surgery, but they treated their patients with six retrobulbar injections [15]. Safi et al. gave two retrobulbar injections after debridement, and Mekonnen et al. treated their patients with three daily retrobulbar injections of L-AMB after endoscopic sinus debridement [14, 18]. So, we can say timing and number of injections cannot be the same in all patients but should be customized based on clinical and radiological findings. The parameters which showed improvement/resolution were lid edema, conjunctival chemosis, extraocular movements, and visual acuity, which were statistically significant. Hirabayashi et al. and Ashraf et al. also reported improvement in visual acuity after TRAMB; the reason may be the improvement in the orbital disease, leading to better perfusion to the optic nerve, which leads to the better visual outcome [15, 17]. The authors reported mild adverse reactions after TRAMB, which were yellow tint chemosis in the inferior part and congestion in a few patients. Safi et al. also experienced the same response in their patients [14]. Hirabayashi et al. reported persistent inflammation after the third injection [15]. Brodie et al. reported acute orbital compartment syndrome following fifth retrobulbar injection; the authors did not observe any such adverse reaction in this study [20].

Out of the 22 patients in the study, exenteration was done in one patient, and one patient died even after TRAMB, which may be due to advanced disease with intracranial extension and their severe altered immunity, which could not prevent the spread of infection. Bayram et al. treated 11

patients of ROCM with retrobulbar L-AMB, out of which three patients had an intracranial extension at the time of presentation, but a total of seven out of eleven patients died due to intracranial extension of disease [19]. From this case series authors reported halting of orbital disease in twenty patients after TRAMB injection, so, it is evident that the Transcutaneous Retrobulbar Amphotericin B injection can play a vital role in preventing the progression of Rhino-orbital Mucormycosis. Hirabayashi et al. also concluded that injecting Amphotericin B in retrobulbar space can halt the progression of the infection in cases where the burden of the disease is not substantial [15]. Safi et al. in their case report described the resolution of cerebritis following administration of retrobulbar Amphotericin B [14].

Conclusion

ROCM is a catastrophic infection with high mortality and requires a multi-disciplinary management protocol. The TRAMB injections are a unique, viable, and potentially globe-sparing approach for selected cases of ROCM. This study may help in guiding the management protocol for ROCM patients, and TRAMB should be considered an option before exenteration. TRAMB seems to be an effective modality to stop the progression of the disease in stages 3a,3b, and 3c but maybe not be suitable for stage 3d and stage 4. Proper patient selection, timely management, and the immune status of the patients play a vital role in achieving the sound effects of the injection. So, it can be an adjuvant therapeutic option to preserve the globe, but definitely, it is not at all replacement for exenteration.

The limitations of this study are that it is retrospective; hence, the patient selection criteria were not uniform and a small sample size. Isolated effects of the TRAMB are difficult to prove because of the additional simultaneous intravenous liposomal Amphotericin B injection and sinus debridement.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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