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Outcome of transcutaneous retrobulbar injection of liposomal amphotericin B in post-COVID-19 rhino-orbito-cerebral mucormycosis: Our experience

Lakshmi B Ramamurthy, Ridhi Bhandari, Savitha Kanakpur, Thejaswini P

Purpose: To assess the outcome and response of transcutaneous retrobulbar injection of amphotericin B (TRAMB) in post-coronavirus disease of 2019 (COVID-19) rhino-orbito-cerebral mucormycosis (ROCM) and to establish a scoring system in guiding treatment modalities. **Methods:** An interventional, prospective study was done on 82 eyes of post-COVID-19 ROCM from May 2021 to July 2021. A comprehensive multi-departmental evaluation along with detailed ophthalmic examination, laboratory investigations, and radiological examination was done. Scoring points were given to each symptom, sign, and radiological features of orbit and the total score was taken. Based on these scores, severity of disease was grouped into A, B, and C corresponding to mild, moderate, and severe orbital ROCM. One milliliter of reconstituted liposomal amphotericin B was given to all patients every alternate day as three doses. Efficacy of these injections was assessed in all groups, even though other treatment modalities like orbital debridement and exenteration were considered for moderate and severe cases. Patients were followed up for a period of 8 weeks. **Results:** Out of 82 eyes, symptomatic improvement was seen in a major proportion (72%) of patients. A statistically significant improvement in scores was noted in group A (93% improved) with a *P* value of 0.002, while 68.4% showed improvement in group B (*P*-value- 0.0001). Group C with severe disease showed minimal improvement in post-injection scores of 41% (*P*-value 0.086), necessitating surgical intervention. No serious adverse effect of the drug or procedure was noted. **Conclusion:** Significant improvement in scores of groups A and B highlights TRAMB as an effective and safe treatment modality in mild to moderate ROCM. It is an effective adjunct in severe cases, along with other interventions. Also, the scoring system helps in assessing the severity and guiding in management strategies.

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Amidst this challenging phase of tackling with the second wave of coronavirus disease of 2019 (COVID-19), here we stand against yet another hassle of the formerly obscure, but notoriously fatal disease, rhino-orbital-cerebral mucormycosis (ROCM).[1] Mucormycosis is a potentially lethal, angioinvasive fungal infection predisposed by diabetes mellitus, corticosteroids and immunosuppressive drugs, primary or secondary immunodeficiency, hematological malignancies and hematological stem cell transplantation, solid organ malignancies and solid organ transplantation, iron overload, etc.[2] The increasing incidence of ROCM in the setting of COVID-19 in India and elsewhere has become a matter of immediate concern. These patients are more prone to ROCM due to the associated comorbidities (e.g., diabetes mellitus, chronic obstructive pulmonary disease), need for oxygen administration, and immunocompromised conditions (e.g., corticosteroid therapy, ventilation, intensive care unit stay). Susceptible individuals develop fungal infection in the paranasal sinuses that can directly invade the orbit and brain.[3] Mucormycosis induces vascular thrombosis, resulting in poor penetration of systemic antifungals.

Currently, there are no standard treatment guidelines. The most widely accepted therapy includes parenteral antifungal therapy and surgical debridement of sinuses.[4] Options for the orbit include exenteration, conservative debridement with irrigation (CDI), and transcutaneous retrobulbar injection of amphotericin B (TRAMB).[5] Injection of retrobulbar liposomal amphotericin B (L-AMB) is an alternative approach that provides local administration to the infected tissues. The adjunct use of antifungal retrobulbar injections has not been extensively reviewed in treating sino-orbital infection.[6]

Herein, we report 82 eyes with ROCM treated with TRAMB in conjunction with systemic antifungals and endoscopic sinus debridement with a goal of establishing TRAMB as a potential globe-sparing intervention for orbital mucormycosis.

With this background in mind, we assessed the epidemiologic data of those who are undergoing TRAMB and categorized patients based on the severity of orbital involvement requiring

Department of Ophthalmology, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India

Correspondence to: Dr. Ridhi Bhandari, #26-27, Mathoshree, Belvanky Colony, Kusugal Road, Keshwapur, Hubli, Karnataka, India. E-mail: ridhiinpyramids@gmail.com

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TRAMB. We also aimed to detect the subjective and objective responses and assess the safety of TRAMB.

Methods

This is an interventional, prospective study conducted from May 2021 to July 2021 on 75 patients with post-COVID-19 ROCM at a tertiary care hospital after obtaining institutional ethical clearance for the study. The study adheres to the guidelines of the Declaration of Helsinki. Severity of the disease involving orbit was assessed and staged based on clinical symptoms, signs, and radiological findings.

At presentation, all patients were subjected to multispecialty evaluation, which included otorhinolaryngology (ENT), ophthalmology, general medicine, and nephrology. Initial ENT evaluation included direct nasal endoscopy (DNE) along with nasal swab collection, which was sent for potassium hydroxide (KOH) mount. Ophthalmic evaluation included visual acuity assessment, pupil reaction, slit-lamp examination, and fundus examination along with grading of ptosis, proptosis, and extraocular motility. Both COVID-19-positive and -negative patients presenting with ROCM were included. Old records of recovered COVID-19 patients were obtained for details like hospitalization, oxygen dependency, vaccination status, and steroid use. All patients were subjected to repeat throat swab for COVID-19 infection.

Predisposing factors for invasive fungal infection were noted. To estimate the magnitude of immune suppression, clinical notes and laboratory values were reviewed. Investigations included: Glycated hemoglobin [HbA1C], fasting and post prandial blood sugar values for diabetes mellitus, serology for immune-compromised status like human immuno deficiency virus[HIV] and hepatitis B [HbsAg] and COVID-19 alarm markers. Imaging included contrast magnetic resonance imaging (MRI) of paranasal sinuses with orbit and brain.

Patients underwent functional endoscopic sinus surgery (FESS) under general anesthesia, and tissues were sent for histopathologic examination. All patients received 50 mg (5 mg/ml) of amphotericin-B (AMB) intravenously (IV). Five hundred milliliters of saline flush was given prior to infusion to prevent renal toxicity.

Being a referral center for post-COVID-19 ROCM, we had a huge load of patients with varying severity. Therefore, we made a working staging system based on clinical symptoms, signs, and radiological features of orbit with specific scores for each of them [Table 1]. Then total scores for each patient were calculated and categorized into groups A, B, and C [Table 2]. For simplicity of further discussion, it can be assumed that group A had mild and early orbital involvement, while group B had moderate and group C had extensive orbital ROCM.

Patients with minimal orbital disease classified under groups A and B were considered for TRAMB. Although the need for surgical interventions for group C were kept in mind, TRAMB was still administered in view of reducing the disease load as well as to buy time as there was a huge surgical load. Orbital disease in COVID-19-positive patients and those who were oxygen dependent were also considered for TRAMB. Disease that was restricted only to paranasal sinus, patients not consenting for the procedure, those with drug allergy, and non-COVID-19 ROCM patients were excluded.

Injection protocol

Preparation: To a vial (50 mg) of L-AMB, 10 ml of distilled water was added to make a concentration of 5 mg/ml; 0.7 ml of this was withdrawn and diluted to a concentration of 3.5 mg/1 ml by adding 0.3 ml of 5% dextrose.

Technique: Prior informed consent of the patients was taken. Under all aseptic precautions, 1.5-inch-long 26-gauge needle was used to deliver 1 ml of 3.5 mg of L-AMB to the retrobulbar space, with injection directed toward the region of radiographic disease in orbit. Gentle pressure was applied to the eyes, and patients were observed for 5 min after injection to monitor for signs of orbital compartment syndrome and reassessed after 4 h of the procedure. Patients received three doses of TRAMB on alternate days and were then reassessed for the disease status. Patients were reassessed after 1 week for persisting signs and symptoms for which two repeat doses were given at an interval of 48 h.

Repeat MRI was done at week 4 [Fig. 1]. Patients who showed further worsening of clinical disease and radiological features were considered for other options like surgical debridement or exenteration. Statistical analysis was done using *t*-test for pre- and post-TRAMB scores in each group, and descriptive data was analyzed in percentages.

Results

A total of 82 eyes (75 patients) were included in the study. Out of them, 22 (29.3%) were females and 53 (70.66%) were males. Sixty-eight (90.66%) patients had unilateral and seven (9.33%) patients had bilateral orbital involvement.

Twenty-six (31.7%, n = 82,) eyes had a visual acuity of negative perception to light (PL −) at presentation, six (7.3%) eyes had vision ranging between perception of light and hand movements, 10 (12.1%) eyes had vision ranging between hand movements [HM] and counting finger [CF] at 3 meters, and 40 (48.7%) eyes had vision more than CF 3 m.

Out of 82 eyes, 64 (78.04%) received three doses, 15 (18.29%) received five doses, and three (3.65%) received less than three doses of TRAMB as they had systemic worsening and succumbed to the disease. Bilateral disease was seen in seven patients, and so, they received TRAMB to both eyes.

Out of 56 eyes with vision ranging from PL + to >CF 3 m at presentation, 50 (89.29%, n = 56,) eyes retained the same visual acuity after TRAMB and two (3.57%) eyes showed improvement from PL + to hand movements. Two (3.57%) eyes lost the vision secondary to disease progression and two (3.57%) were lost to follow-up due to their demise.

Out of 82 eyes, symptomatic improvement with respect to pain was seen in 59 (71.9%) eyes, reduction of eyelid swelling in 48 (58.53%) eyes, and improvement in drooping of eyelids in 17 (20.73%) eyes. Improvement in signs like ptosis was noted in 10 (12.1%) eyes, proptosis reduction was noted in five (6.09%) eyes, reduction in chemosis was noted in 11 (13.41%) eyes, and improvement in ocular motility was noted in 14 (17.07%) eyes [Table 3 and Fig 2].

Improvement was assessed objectively by giving scores before TRAMB and after 8 weeks of TRAMB. Based on the scoring system followed, there were 15 patients in group A, 38

Table 1: Scoring system followed for categorizing the patients, which included clinical symptoms, signs, and radiological findings

Symptoms	Points	Signs	Grading	Points
Pain	1	Vision	PL–	3
			PL+to HM+	2
			HM+to CF 3 m	1
			>CF 3 m	0
Eyelid swelling	1	Ptosis	Mild	1
			Moderate	2
			Severe	3
Drooping of eyelid	2	Proptosis	<21 mm	0
			21-23 mm	1
			23-25 mm >25 mm	2
				3
Blurring of vision	2	Soft tissue signs	Chemosis	1
			Conjunctival congestion	1
		Ocular motility	WNL	0
			–1	1
			–2	1
			–3	2
			–4	3

Fundus findings	Scores
CRAO/AION	3
Retinal detachment/infiltrates	2
Vein occlusion/vascular changes	1
Normal fundus	0
MRI findings	
Grade 1	
Within normal limits	1
Extraconal fat stranding	1
EOM bulkiness	1
Good contrast uptake	1
Grade 2	
Single compartment	1
Altered contrast uptake	1
>1 compartment + retro-orbital fat stranding	1
SOV dilation	1
Grade 3	
Orbital abscess	2
Orbital apex involvement	2
Optic nerve involvement	2
Orbital wall erosions	2
SOV thrombosis	3
Cavernous sinus thrombosis	3

MRI=magnetic resonance imaging, CRAO=Central retinal artery occlusion, AION=Anterior ischemic optic neuropathy, EOM=Extra Ocular muscles, SOV=Superior ophthalmic vein, HM=Hand movements, PL=Perception of light

Table 2: Grouping of patients based on scores for categorization of disease

Group	Symptom	Score
Group A	Early or mild orbital component of ROCM	<10
Group B	Intermediate or moderate orbital ROCM	10-19
Group C	Extensive orbital involvement of ROCM	≥20

ROCM=rhino-orbito-cerebral mucormycosis

in group B, and 29 in group C. Pre-TRAMB and post-TRAMB scores for all three groups were analyzed using *t*-test. Mean pre-TRAMB scores were 7, 13, and 23 in groups A, B, and C, respectively. Post-TRAMB scores reduced significantly in groups A and B, while group C showed minimal change in scores. Mean post-TRAMB scores were 3, 6, and 20 in groups A, B, and C, respectively [Graph 1]. Fourteen (93.33%) out of 15 eyes showed improvement in group A with significant

Figure 1: Administration of retrobulbar amphotericin for orbital mucor mycosis

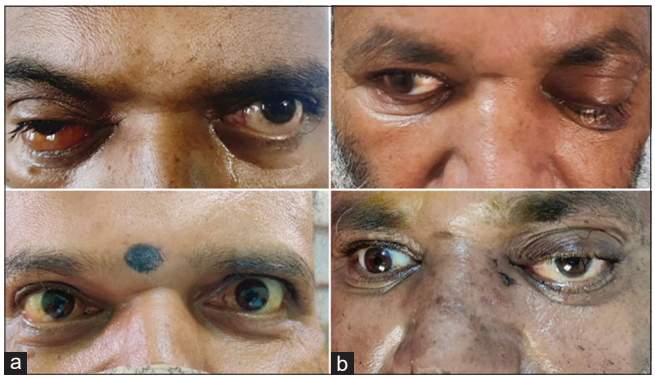
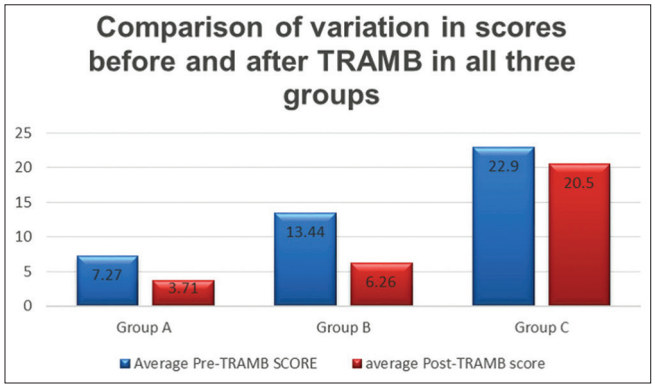


Figure 2: (a) Comparison of pre- and post-TRAMB in a patient with right-sided ROCM, showing significant improvement in ptosis and chemosis. (b) Comparison of pre- and post-TRAMB in a patient with left-sided ROCM, showing marked improvement in ptosis with partial resolution of proptosis. ROCM = rhino-orbito-cerebral mucormycosis, TRAMB = transcutaneous retrobulbar injection of amphotericin



Graph 1: Variations in pre- and post-TRAMB scores in all the groups. TRAMB = transcutaneous retrobulbar injection of amphotericin

Table 3: Improvement of clinical signs and symptoms after TRAMB

	Number of patients	Percentage
Retained/improved vision	52	63.41
Pain relief	59	71.9
Reduced swelling/lid edema	48	58.53
Improvement of drooping	17	20.73
Reduced chemosis	11	13.4
Reduced proptosis	5	6.09
Reduced ptosis	10	12
Improved ocular motility	14	17.07

TRAMB=transcutaneous retrobulbar injection of amphotericin B

P value (*P* = 0.00215) after TRAMB. Twenty-six (68.4%) eyes out of 38 eyes in group B had significant improvement (*P* = 0.0001), seven (18.42%) eyes showed minimal improvement, three (7.89%) eyes were status quo, and two (5.26%) eyes showed worsening. In group C, 12 (41.37%) eyes showed minimal improvement in post-TRAMB scores; however, the difference was not statistically significant (*P* = 0.086).

Four (4.87%) eyes developed swelling at the site of injection, which can be attributed to local inflammatory reaction due to the drug itself. It eventually resolved with the local antibiotic treatment and analgesics. Two (2.43%) eyes had worsening of vision and ocular motility following three doses. One (1.21%) eye had retinal infiltrates near the optic disk, which regressed in size eventually. It could possibly be due to the disease progression.

Nineteen (23.17%) eyes developed transient orbital inflammation with increase in chemosis and conjunctival congestion. Subsequent doses were withheld, and the schedule was restarted after resolution of the same, which was within a span of 36 h. No alterations in intra-ocular pressure[IOP] and vision were noted.

Patients who showed worsening and needed further intervention were considered for surgery. In group B, three patients underwent orbitotomy and debridement with AMB irrigation and two patients needed exenteration. Patients in group C needed more of surgical intervention. Seven patients underwent orbitotomy and debridement with AMB irrigation and in 10 patients, exenteration was done. This reflects that more severe disease would warrant surgical intervention, and TRAMB in them would help to buy time while awaiting surgery or they are being referred for a higher center, where it might help in halting the disease progression. At 8 weeks follow-up, we lost four patients, while 71 patients were alive with a survival rate of 94.6%.

Discussion

The current scenario of ROCM in the setting of COVID-19 in India and elsewhere is alarming and has posed multiple challenges along with dealing with the COVID-19 pandemic.[6,7] In this study, we have categorized post-COVID-19 ROCM patients using a scoring system that has been adopted based on clinical and radiological evidence and we have analyzed the effect of TRAMB in these patients.

Considering the demographics, our patients' age ranged between 23 and 68 years with a mean of 49.2 years and showed a male preponderance. An epidemiological multicentric study done in India reports comparable age category with the mean being 52 years.[8] Mean age was found to be lower when compared with previous reported data in pre-COVID-19 era. This could be attributed to post-COVID-19 alterations in immune status and post-COVID-19 precipitation of diabetes. Male predisposition was noted, as similarly reported in other studies.

Patients with orbital involvement have a higher mortality than those with sinus-only disease.[9] Multiple reports have been published regarding the treatment protocols and local administration of amphotericin for invasive fungal sinusitis with orbital involvement. Seiff *et al*.[10] described conservative orbital debridement with local AMB irrigations as an effective adjunct in the control of sino-orbital fungal infections. Evan Kalin-Hajdu *et al*.[5] described three treatment options for orbital fungal infection: exenteration, conservative debridement with local irrigation, and TRAMB. Guidelines by Code Mucor, published during the epidemic of post-COVID-19 mucor, also propose TRAMB for early orbital involvement in post-COVID-19 mucormycosis.[1] In a multicentric study from India considering 127 post-COVID-19 mucormycosis cases, retrobulbar injection was effective in four out of five patients as a globe-sparing regimen.[11] All the above-mentioned reports have documented the effect of deoxycholate AMB injection, while we have analyzed L-AMB in our study. Based on the available literature and in this current situation of sudden spike of post-COVID-19 ROCM, we considered local drug delivery with L-AMB and analyzed the outcome.

Local injection of AMB has been shown to resolve intra-articular, intrapleural, and intranasal fungal infections.[12-14] Saedi *et al*.[12] documented the added advantage of topical amphotericin-soaked cottonoid pledgets in FESS for efficient outcome, along with debridement and systemic antifungals. Irrigation of orbital tissues with AMB via a catheter has been well described.[12,15] The benefit of locally administering AMB is predicated on the angioinvasive nature of the disease that limits tissue penetration of systemic antifungals. Ibrahim *et al*.[16] demonstrated that *Rhizopus* spores and germ tubes adhere to and damage human endothelial cells. This injury results from direct contact between the fungus and the endothelium and subsequent phagocytosis of the fungus. In addition, AMB diffuses slowly into tissues due to its high protein-binding capacity and large molecular weight.[3,16] Hence, local TRAMB can reach those tissues with higher ability than the IV antifungals alone.

Ashraf *et al*.[2] compared the outcome of modified treatment algorithm with incorporation of TRAMB into orbit after 2015 in their study. They had used modified ladder algorithm approach for treating invasive fungal sinusitis with orbital involvement, which showed similar mortality rates with TRAMB as with surgical intervention practiced before, thus analyzing TRAMB as a globe-sparing intervention. On evaluating our data, we could observe that TRAMB is an effective treatment modality in early orbital involvement and an effective globe-sparing regimen when combined with debridement of orbit and sinuses in moderate disease.

Shah *et al*.[17] analyzed a scoring system for consideration of ROCM patients for exenteration, which included clinical signs and symptoms, fundus findings, and imaging. Similarly, we wanted to categorize the patients for appropriate management. Hence, we formulated all the clinical symptoms, signs, and radiological data into a grading system and incorporated this data into patients receiving TRAMB for better analysis and interpretation. Based on the scoring system followed, there were 15 patients in group A, 38 in group B, and 29 group C.

Most patients with early orbital involvement belonging to group A had statistically significant decrease in post-TRAMB scores, suggesting good recovery. Hence, TRAMB can be considered as the only therapeutic modality for early or minimal orbital involvement. Considering the patients in group B, we noticed that there was a good response in a significant number of patients. Thus, TRAMB can be considered as an initial and adjuvant therapeutic option for intermediate ROCM (group B) and when combined with adequate debridement, it proves to be a globe-sparing intervention. When considering patients in group C, only 12 eyes showed minimal improvement and 17 patients needed surgical intervention. Hence, TRAMB can considered as a viable option for treating physicians in the periphery to slow down the progression of disease and for buying time to refer them to higher centers for surgical intervention. Also, at the tertiary hospitals, with surging cases of mucor and a huge surgical load, this can be considered as an effective way to prevent worsening while awaiting surgery as well as in patients who are COVID-19 positive or oxygen dependent, in whom the risk of general anesthesia is high.

It is to be noted here that retrobulbar injection of amphotericin is off-label till date and has its associated risks. Though many reports have documented successful treatment without any serious adverse effects,[2,3] the drug per se is known to known to incite tissue inflammation and the potential of neurotoxicity as *in vitro* studies have shown cytotoxic effects.[18] In comparison, we had three cases of local swelling at the injection site and inflammatory response, which subsided in due course of time.

In our study, we have treated all the patients with functional endoscopic sinus debridement and IV amphotericin, along with the treatment modalities explained for orbital disease. Hence, these may act as confounding factors. We have used L-AMB in our study, while most of the studies have described deoxycholate amphotericin for TRAMB.[3,5] Our proposed scoring system is being applied to a small set of data, and hence requires larger data to further strengthen this. Considering the small sample size with a short follow-up period, this study would further need supportive large data studies with longer follow-up.

Conclusion

TRAMB is a very effective, economical, time-saving procedure in patients with orbital mucormycosis of mild to moderate severity. In the early form of disease, it can be considered a less-invasive efficient strategy to prevent disease progression as well as to cure it. Also, it aids to buy time by halting the disease progression in patients who need surgical intervention but cannot undergo the same due to unavailability of services at the peripheral set-ups, in systemically unstable patients, and also in centers with a high surgical load.

In instances where systemic antifungal supply is scarce, patients who underwent FESS and have early orbital

involvement, it could be a potential source of treatment requiring less dose, covering more patients and prevents disease worsening. To conclude, this study could be a guiding light to fellow ophthalmologists with limited experience of ROCM for better decision-making, and thus saving life and vision.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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