

Transcutaneous retrobulbar amphotericin-B (TRAMB) injection in orbital mucormycosis

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SUMMARY

We aim to highlight the role of transcutaneous retrobulbar amphotericin-B (TRAMB) in cases of rhino-orbital mucormycosis. With the COVID-19 pandemic a rapid surge in the number of cases of rhino-orbital mucormycosis has been noted. The gold standard treatment for the progressive orbital disease is exenteration; however, organ salvage should be attempted, when possible. Here comes the role of TRAMB injection. We present a case of a man in his 70s, a known diabetic, who recovered from COVID-19 pneumonia but developed left-sided axial proptosis with orbital apex syndrome and ophthalmic artery occlusion secondary to rhino-orbital mucormycosis. The patient underwent debridement of paranasal sinuses and received intravenous liposomal amphotericin-B and three TRAMB injections. After three TRAMB injections significant improvement in extraocular movements, proptosis and ptosis was noted. An early intervention in orbital disease can avert a more radical procedure.

BACKGROUND

Rhino-orbital mucormycosis is a rapidly progressive and potentially lethal angioinvasive fungal sinusitis exclusively affecting immunocompromised individuals. In the current scenario of COVID-19, diabetes mellitus, indiscriminate use of systemic steroids and immunosuppression caused by COVID-19 itself have been identified as major factors attributing to epidemic of mucormycosis.¹ Angioinvasion leads to thrombosis and distal ischaemia which further causes necrosis. Management includes correction of the underlying immunocompromised condition, aggressive debridement of paranasal sinuses with or without limited orbital debridement and in diffuse orbital involvement exenteration along with the systemic antifungals.^{2,3} In orbital diseases local injection of liposomal amphotericin-B in the intraconal space (before the tissues lose viability) is a valuable option. This facilitates higher drug concentration reaching to the required site without causing systemic side effects. Orbital exenteration can be averted if timely transcutaneous retrobulbar amphotericin-B (TRAMB) injection is given.⁴ This report gives an insight on having a larger trial on TRAMB for cases of rhino-orbital mucormycosis.

CASE PRESENTATION

An old man in his 70s, recovered from COVID-19 pneumonia, was presented to the ophthalmology OPD with complaints of pain, swelling, protrusion and drooping of left upper lid for 1 week. The patient had sudden deterioration of vision in the left

eye since last 2 days. His examination revealed left eye visual acuity to be perception of light with inaccurate projection of rays. The right eye was essentially normal; however, there was axial proptosis, complete ptosis and total limitation of extraocular muscle movements of the left eye ([figure 1A](#)). There was decreased supraorbital and infraorbital sensations along with decreased corneal sensation on the left side. Significant conjunctival chemosis and a left eye relative afferent pupillary defect was also noted. The dilated fundus examination showed whiteout retina with cattle trucking of blood vessels and arteriolar attenuation in the left eye ([figure 1B](#)). An otolaryngologist consult was sought and was on diagnostic.

Diagnostic nasal endoscopy (DNE) showed eschar over both the middle meatus ([figure 1C](#)). The nasal swab for KOH mount from the same revealed broad aseptate hyphae suggestive of mucormycosis. The contrast enhanced-magnetic resonance imaging (CE-MRI) orbit, paranasal sinuses and brain showed diffuse orbital enhancement (including apex) and enhancement of ethmoidal sinuses suggestive of rhino-orbital mucormycosis ([figure 2](#)). Magnetic resonance angiogram showed ophthalmic artery occlusion.

The patient had undergone extensive debridement of maxillary and ethmoid sinuses by external approach and also received intravenous liposomal amphotericin-B (LAMB) (5 mg/kg) after a baseline evaluation of renal and hepatic functions. The patient received intravenous amphotericin-B for 14 days. A total of three doses of transcutaneous retrobulbar amphotericin-B (TRAMB) injections (1 mL of 3.5 mg/mL) were given to the patient for three consecutive days. After three TRAMB injections, there was initial increase in the periorbital swelling; however, subsequently it was noted that the patient had improvement in extraocular movements, reduction of proptosis and improvement in ptosis; however, there was no improvement in vision ([figure 3](#)). The patient was stable systemically thereafter till the last follow-up at 3 months.

OUTCOME AND FOLLOW-UP

At 3 months follow-up the patient had significant improvement in ptosis, proptosis and extraocular movement; however, there was no improvement in vision in the affected eye.

DISCUSSION

TRAMB injection is not a newer modality and has been in use for invasive orbital aspergillosis.⁵ Considering the more fulminant course of the



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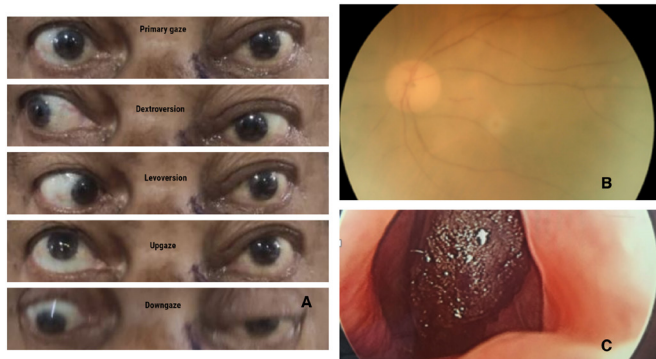


Figure 1 (A) Clinical picture showing limited ocular motility on the left side. (B) Shows retinal whiteout appearance due to ophthalmic artery occlusion. (C) Diagnostic nasal endoscopy finding showing eschar over turbinate.

orbital mucormycosis and its propensity to cause thrombosis and tissue necrosis, it is worth giving a try to TRAMB injection. A thorough literature search was done and isolated reports on transcutaneous retrobulbar amphotericin B were found even for mucormycosis. There is no robust evidence either in support or against it. A case report published by Kristin *et al* showed that the retrobulbar amphotericin-B halted the progression of orbital infection. The author considered it a viable treatment option in case of early rhino-orbito-cerebral mucormycosis.⁴ Another case reports by Mustafa *et al* found TRAMB as an effective adjuvant treatment modality averting exenteration in a patient with rhino-orbital-cerebral mucormycosis (ROCM) with cerebritis.⁶ Kalin-Hajdu *et al* proposed a management algorithm based on the imaging of orbital soft tissue and clinical examination. They justified the role of retrobulbar amphotericin-B in early orbital disease and suggested radical procedure like exenteration only when the disease worsened.⁷ In our case patient received standard treatment. The patient underwent sinus debridement and limited orbital debridement. The patient also received

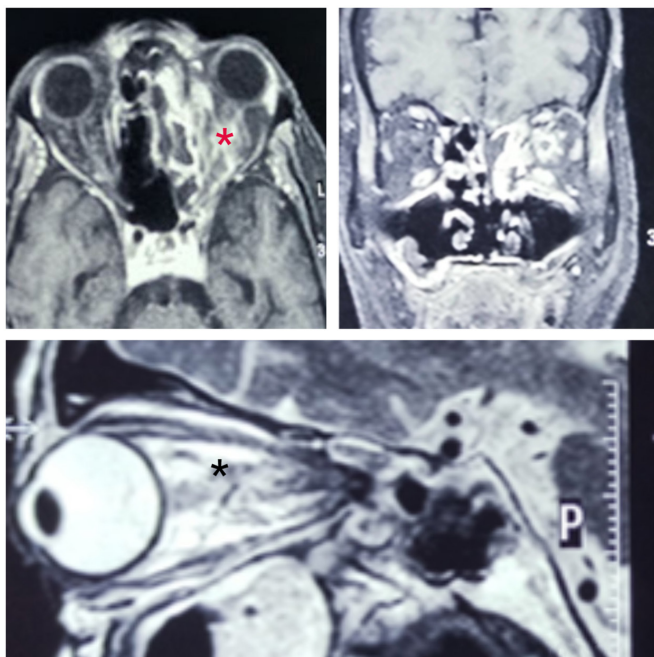


Figure 2 MRI showing diffuse orbital enhancement and intraconal fat stranding.

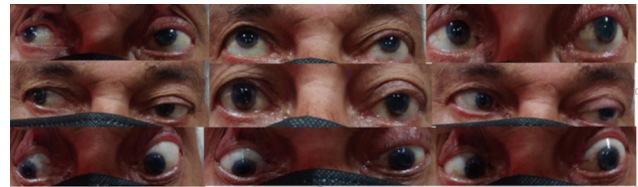


Figure 3 Clinical improvement in extraocular motility after receiving three doses of TRAMB.

intravenous amphotericin-B (5 mg/kg). In view of severe visual loss incurred by orbital mucormycosis along with intraorbital fat-stranding associated with cranial neuropathies, intraorbital amphotericin-B was given as an additive treatment to the patient. Our inclusion criteria for intraorbital amphotericin-B injection were moderate to severe visual loss, and/or subtle localised orbital enhancement (on MRI) with cranial neuropathy (II, III, IV, V, VI), and/or moderate to diffuse orbital enhancement or apical enhancement of orbit on contrast MRI, and/or loss of enhancement of surgically accessible orbital area (not involving apex). These criteria were consistent with the criteria proposed by Hirabayashi *et al*⁴ In another study by Ashraf *et al*, patients who received TRAMB injection had lower risk of exenteration compared with the historical controls.⁸ Nair *et al* summarised all the previous published reports or series on TRAMB injections and proposed a treatment algorithm based on radiological and clinical findings.⁹ Our report further substantiates the role of retrobulbar amphotericin-B in facilitating clinical recovery in cases of ROCM. Neurological involvement warrants the use of higher doses of intravenous amphotericin-B, which is associated with severe systemic adverse reactions like hypokalaemia and renal dysfunction. The use of TRAMB injection in our case was an attempt to minimise the adverse reactions of high dose intravenous amphotericin-B and simultaneously address the orbital disease. In our case, the patient was planned for a total of six retrobulbar amphotericin-B injections; however, considering the development of significant periorbital oedema following three injections, further injections were curtailed. Though, the oedema subsided over 1 week. Subsequent doses were withheld in view of improvement noticed with three doses itself. In our report, clinical recovery was defined as improvement in ptosis, decrease in proptosis and recovery of extraocular motility. The retrobulbar amphotericin-B when given locally at an early stage (only enhancement but no necrosis), the radical procedures like exenteration can be averted.

Learning points

- ▶ Considering the large number of cases of rhino-orbital mucormycosis we as medical fraternity should look for less invasive and less radical surgical options. And transcutaneous retrobulbar amphotericin-B is a viable option in the early cases of orbital disease when the vitality of tissue is still not compromised.
- ▶ Local high concentration of amphotericin-B avoids systemic side-effects and also obviates the need for future exenteration.
- ▶ A large trial is the need of the hour and would further pave our way and generate a stronger evidence on role of transcutaneous retrobulbar amphotericin-B.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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