

## Retrobulbar injection of amphotericin B using intravenous cannula for post-COVID-19 rhino-orbital mucormycosis

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Rhino-orbital mucormycosis has seen a huge resurgence in patients post COVID-19 infection. In patients with minimal orbital disease and especially with preserved vision, retrobulbar injections of amphotericin B can be of great help in controlling the disease. Instead of giving daily injections of amphotericin B using needles every time, we used an 18-gauge intravenous (IV) cannula with injection port and suture holes to deliver the amphotericin into the orbital space for a period of 5 days. Patients were more compliant and less distressed with this method compared with being given an injection with a needle daily. We got a good response in terms of orbital disease regression with this method. In our review of the literature, we did not come across any such case of amphotericin B injection using an IV cannula. Injection of amphotericin B into the orbit using an IV cannula is a viable and easy treatment option for cases of rhino-orbital mucormycosis.

**Key words:** Amphotericin B, intravenous cannula, rhino-orbital mucormycosis

Rhino-orbital mucormycosis has assumed pandemic proportions in post-COVID-19-infected patients. The fungus causes vascular thrombosis and hence penetration of the antifungal drugs given intravenously is inadequate. Therefore, surgical debridement needs to be done along with systemic antifungals.<sup>[1]</sup> With the aim of avoiding exenteration and conserving the eye, retrobulbar injections of amphotericin B are given for its fungicidal properties.<sup>[2-5]</sup> Using a long intravenous cannula can be effective in ensuring drug delivery into the orbit, and this obviates the need for daily injections with

syringes. We used an 18-G intravenous cannula with injection port and suture holes to deliver the amphotericin into the orbit for a period of 5 days. To the best of our knowledge, this has not been reported in the literature. We did not encounter any blockage of the cannula or secondary infection in these patients. Patient comfort and compliance were satisfactory with this modality of drug delivery.

### Case Reports

#### Case 1

A 69-year-old male presented to the emergency department with complaints of right side upper molar pain and eye swelling for 4 days. The swelling was sudden, progressive, and extending to the cheek. He also had difficulty opening his right eye. He was a diabetic since the last 20 years on insulin and oral antidiabetic agents. He had contracted COVID-19 infection 1 month back, needed oxygen, and was administered steroids intravenously for 10 days. He underwent endoscopy by the ENT surgeon, and mucormycosis was confirmed on histopathological examination of the nasal crusts with calcofluor white and he was referred to the oculoplasty service. Examination revealed vision 6/9 in each eye with glasses. The left eye was normal. The right eyelid had diffuse edema, complete ptosis, and abduction limitation (-2) was present. There was proptosis of 3 mm. Anterior segment examination revealed pseudophakia, conjunctival chemosis, and congestion [Fig. 1a]. MRI scan revealed the presence of T2 hypointense soft tissue in the frontal and ethmoid sinuses with extension into the medial orbit suggestive of fungal invasion. While he was undergoing endoscopic sinus surgery, an 18-gauge, 1<sup>3/4</sup> inch (1.3 × 45 mm) intravenous cannula with injection port and suture holes, manufactured by B Braun Melsungen AG, with a Vasofix Braunule Luer Lock system, was inserted superomedially in line with the inner canthus into the retrobulbar space as we would normally give a peribulbar injection and was sutured to the skin of the upper eyelid [Fig. 1c and d]. He received five injections of amphotericin B (deoxycholate form; 10 mg in 2 ml) daily. He also continued to receive intravenous liposomal amphotericin B 300 mg daily during this period; this was continued for 10 days, after which he was prescribed oral posaconazole for 2 months and advised regular follow-up. There was improvement of the ptosis and reduction of the chemosis and congestion after the injections. At the last follow-up 90 days following the injection, the patient was stable with a vision of 6/12 [Fig. 1b].

#### Case 2

A 56-year-old lady presented with left eye loss of vision, ptosis, lid swelling, and proptosis of 5 days duration. She had

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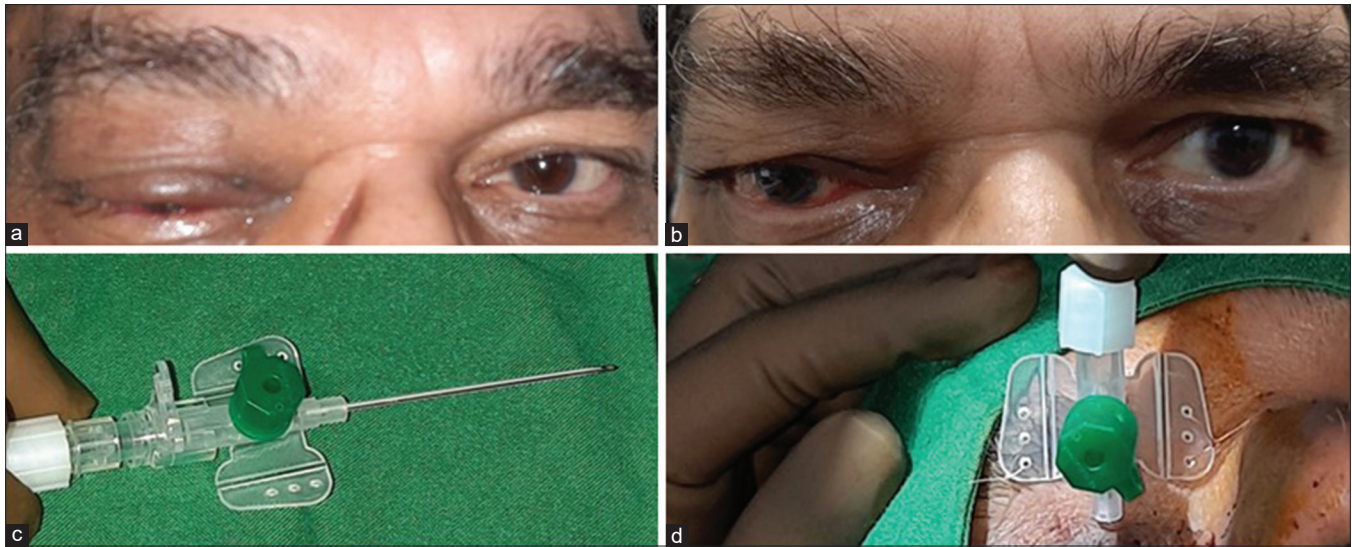
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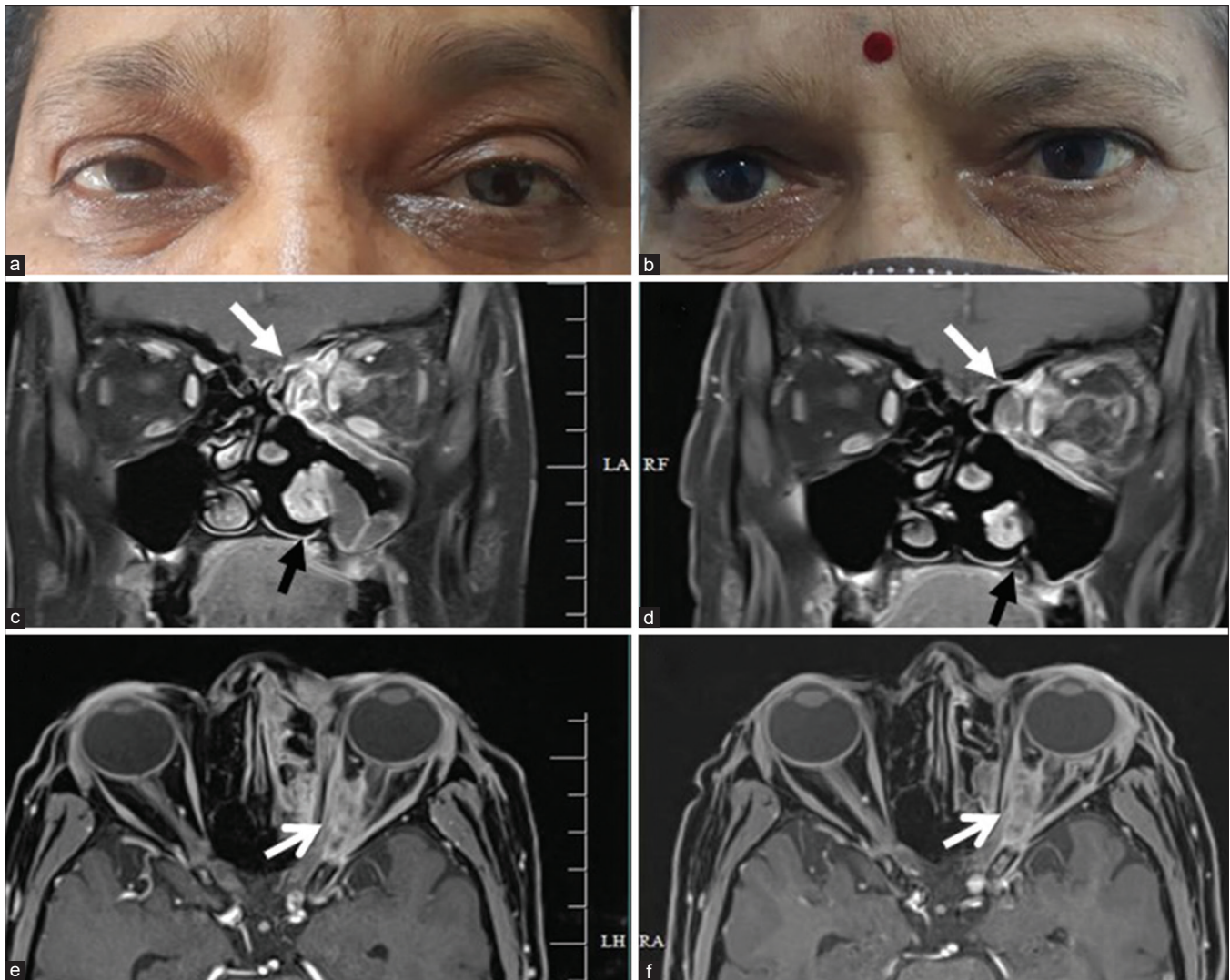
**Figure 1:** (a) A 69-year-old male patient presented with right eyelid edema, ptosis, proptosis, chemosis, and congestion. (b) Following the course of retrobulbar injections of amphotericin B, the lid edema reduced, ptosis improved, and chemosis resolved. (c) An 18-gauge, 1<sup>3</sup>/<sub>4</sub> inch (1.3 × 45 mm) intravenous cannula with injection port and suture holes, manufactured by B Braun Melsungen AG, with Vasofix Braunule Luer Lock system was used. (d) The cannula was sutured to the upper lid with sutures and amphotericin B was injected through the cannula into the orbit

**Table 1: Comparison of various reports of retrobulbar injection of amphotericin B for rhino-orbital mucormycosis**

Study	Clinical presentation	Radiologic involvement	Vision at presentation	Dose of TRAMB/ Route of delivery	Final vision	Outcome at last visit	Follow-up duration
Luna <i>et al.</i> 1996 <sup>[8]</sup>	Total ophthalmoplegia, CRAO	Orbital apex and medial orbital wall	No PL	1 mg/ml for 9 days/ intraorbital intraconal catheter	No PL	Eye preserved, movements better	18 months
Pelton <i>et al.</i> 2001 <sup>[9]</sup>	Pain, swelling, proptosis	Inferior and medial orbit, pterygopalatine fossa	20/25	15 mg twice a day/ surgical packing with amphotericin soaked gauze	20/25	Eye preserved, normal motility	18 months
Hirabayashi <i>et al.</i> 2016 <sup>[5]</sup>	Total ophthalmoplegia, RAPD	Medial wall involvement, enhancement of orbital fat	20/70	1 ml of 3.5 mg/ml for 6 days/retrobulbar injections	20/20	Eye preserved, movements normal	5 months
Seiff <i>et al.</i> 1999 <sup>[13]</sup>	Details not mentioned	Not mentioned	CF@3ft	IV Amphotericin B, intraoperative irrigation 3 ml (1 mg/ml) 3 times a day × 5 days	20/100	Died at 1 month from unrelated causes	1 month
Joos <i>et al.</i> 2017 <sup>[14]</sup>	Left intraorbital abscess	Orbital abscess, sinuses	20/25	Jackson Pratt drain in orbit, 5 ml (1 mg/ml) for 7 days	20/25	Improved ocular motility	18 months without recurrence
Kahana <i>et al.</i> 2007 <sup>[12]</sup>	Orbital pain and diplopia	Orbit, sinuses and brain	Not specified	Intraorbital radioopaque catheter 1 ml (1 mg/ml) 3 times a day × 20 days	Not specified	Died after 16 months due to intraventricular hemorrhage	16 months
Safi <i>et al.</i> , 2020 <sup>[11]</sup>	Proptosis, partial ophthalmoplegia	Medial and inferior orbit	20/20	1 ml of 3.5 mg/ml for 2 days, 3 day gap/ retrobulbar injection	20/40	Partial resolution of eye movements	16 months

been diagnosed as COVID-19 positive on RT-PCR test 11 days ago and was on supplementation oxygen 2 liters/min and had received five doses of intravenous dexamethasone. She was a known diabetic since the last 15 years and was on oral antidiabetic agents. Examination of the right eye was within normal limits. Left eye had proptosis, mild ptosis, upper and

lower lid edema, and lateral rectus palsy with -4 limitation of abduction with no perception of light; fundus examination showed signs of central retinal artery occlusion [Fig. 2a]. MRI scan showed the presence of T2 hypointense soft tissue in the maxillary and ethmoid sinuses and at the intraconal and extraconal location of the left eye orbit with extension



**Figure 2:** (a) A 56-year-old lady presented with left eye ptosis and proptosis since 5 days. (b) Following treatment, at 5 months follow-up, she was fine. (c and e) T1 fat-suppressed post-contrast coronal (c) and axial image (e) shows soft tissue in medial orbit (white arrow), hypointense with peripheral enhancement suggestive of fungus. Similar soft tissue is seen in the maxillary sinus (black arrow). (d and e) After 5 months, T1 fat-suppressed post-contrast coronal (d) and axial image (f) shows significant regression of disease in left maxillary sinus (black arrow) and orbit (white arrow)

to the orbital apex [Fig. 2c and e]. After nasal endoscopy and FESS and confirmation of the diagnosis of mucormycosis, she received intravenous amphotericin B for 3 weeks followed by oral posaconazole for a period of 2 months. Injection of deoxycholate amphotericin B was given transcutaneously through the intravenous cannula in the superomedial orbit daily in the dose of 10 mg in 2 ml for 5 days. Post injection patient developed chemosis with a yellow tinge to the conjunctiva, which resolved in 10 days. At the last follow-up after 7 months, there was no ptosis or proptosis, abduction limitation was - 3 in the left eye; however, there was no light perception [Fig. 2b]. MRI scan revealed significant regression of the disease [Fig. 2d and f].

## Discussion

Exenteration has an adverse psychological impact and causes permanent blindness and facial disfigurement; thus, the

decision to exenterate is often controversial.<sup>[6]</sup> Moreover, post-COVID-19-infected patients have poor immunity and fragile health and may not be able to tolerate such a major surgery. Avoiding orbital exenteration may be prudent many a time as it may not be necessary or may not offer increased chances of life salvage, especially with cerebral involvement.<sup>[5]</sup> Localized fungal infections have been successfully treated by intranasal, intrapleural, and intraarticular administration of amphotericin B.<sup>[7]</sup> Retrobulbar injections of amphotericin B using injections and a catheter inserted during sinus surgery have been successful [Table 1].<sup>[5,8,9,11-14]</sup>

Amphotericin B is a polyene antibiotic that binds to the cell membrane sterols, forming pores, thus causing leakage of intracellular electrolytes and derangement of metabolic activity and cell death.<sup>[10]</sup> Amphotericin B has a large molecular weight and high protein binding and hence diffuses slowly into the tissues. The deoxycholate form has been used for

retrobulbar injections with good results.<sup>[5]</sup> We used the deoxycholate form as the orbit is an enclosed small space and risk of nephrotoxicity does not arise, in addition to the cheaper cost. Placement of an intravenous cannula can help in more diffuse drug delivery.<sup>[9]</sup> A cannula obviates the need for daily injections, increases compliance, and is an easily accessible location. The cannula can be removed once the course of injections is complete. Blockage may occur, though unlikely, as this has a wide bore, in which case it is best to remove the cannula and insert a new one. One cannot be certain about the intraconal position of the cannula, but the needle is approximately 4.3 cm long and rests near the apex of the orbit. Multiple pockets of infection may be difficult to address with a cannula. Amphotericin B is potentially cytotoxic, incites inflammation by expression of proinflammatory cytokines, increases the edema, and may cause toxin neuropathy; this is the reason for the transient inflammation in the form of chemosis we saw after amphotericin B injection and even acute orbital compartment syndrome has been documented.<sup>[3-5,10]</sup>

## Conclusion

The greatest advantage of retrobulbar injection is that it is globe-sparing. Retrobulbar injections using an intravenous cannula are a valuable adjunctive modality to halt the orbital progression and provides an opportunity to avoid exenteration and save the eyeball in cases of rhino-orbital mucormycosis.

## 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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## Conflicts of interest

There are no conflicts of interest.

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