

“A clinical study of Post COVID-19 cases of IFROS(Invasive Fungal Rhino-orbital Sinusitis) , using TRAMB (Transcutaneous retrobulbar Amphotericin-B), at a tertiary care hospital, in South India”.

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Abstract:

The incidence of fungal rhino-orbital sinusitis(IFROS) has increased in post COVID-19 patients. In the present study, a total of 300 pts (360eyes) with IFROS . treated with TRAMB (Transcutaneous Retrobulbar Amphotericin B) are analyzed, retrospectively, at a tertiary care center.

The progression of orbital infection was halted in 70% of the eyes and visual acuity restored with eventual hospital discharge in 20% of the eyes, following TRAMB, globe -saving technique.

Key words: IFROS, TRAMB, Fungal Rhino-orbital Sinusitis, Retrobulbar, Amphotericin B

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I. Introduction:

IFROS (Invasive Fungal Rhino-orbital Sinusitis) is a life-threatening infection associated with high morbidity and mortality¹.

COVID-19 infection increases the risk of a patient acquiring secondary fungal infection due to Diabetes and COVID treatment. Susceptible individuals develop fungal infection in the paranasal sinuses that can directly invade the intracranial and intraorbital spaces².

The symptoms and signs of IFROS included facial pain, sinus headache, stuffy nose, decreased vision, bloody nasal discharge, dental pain, facial swelling, facial discoloration, palatal eschar, nasal eschar. The ophthalmological signs are ptosis, proptosis, central retinal artery occlusion (CRAO) and ophthalmoplegia³.

The current standard of care involves reversal of immune status, debridement of devascularized tissue, and systemic antifungal therapy.

Systemic antifungals alone are typically insufficient for eliminating the infection due to its angioinvasive nature, which leads to obliteration of local blood supply and rapid tissue necrosis that limit the penetration of systemic therapy. Therefore, debridement of necrotic tissue plays a key role in the management of IFROS⁴.

Functional endoscopic sinus surgery (FESS) with biopsy and debridement of affected tissues has a well-established role in the diagnosis and management of IFROS, with improved survival⁵.

Exenteration has classically been used in cases of significant orbital disease, but a definite survival benefit has not been demonstrated⁶.

Some groups have reported the conservative debridement of necrotic tissue, sometimes in conjunction with intraoperative irrigation of amphotericin B, with good outcomes.

Conservative debridement is not always practical, owing to the close proximity of important orbital structures and the limited intraoperative visualization of the orbital apex.

Other groups have reported bedside transcutaneous retrobulbar injection of amphotericin B (TRAMB) as a minimally invasive alternative to surgical treatment with favourable outcomes in a small number of reports⁷.

In our study, the clinical results and the factors influencing the visual outcome, in Post COVID, IFROS cases, treated with TRAMB are presented.

II. Materials and Methods:

Three Hundred consecutive patients with biopsy-proven invasive fungal sinusitis and radiographic evidence of orbital involvement were evaluated at a tertiary care Hospital in coastal districts of AndhraPradesh, from April 2021-July 2021.

TRAMB was incorporated as part of the treatment algorithm in COVID Mucormycosis treatment. Nearly all patients underwent a surgical intervention, which most commonly was functional endoscopic sinus surgery with debridement.

Injection Protocol: The dosage schedule is 3.5 mg of Amphotericin B 3 doses prior to FESS debridement of fungus of all PNS and another 2 or 3 doses of Amphotericin B given to all after operation of FESS debridement of PNS depending upon improvement of ocular problems.

The total number of doses for every patient received are minimum of 3 and maximum of 6.

The inpatient pharmacy provided compounded liposomal amphotericin B at a concentration of 3.5 mg/mL. Patients were anesthetized with a retrobulbar injection of 2 to 3 mL of lidocaine to prevent medication-associated pain. After 5 minutes, a 23-gauge retrobulbar needle was then used to deliver 1 mL of the liposomal amphotericin B to the retrobulbar space, along the medial orbital wall. Gentle pressure was applied to the eyes and patients were observed for 5 minutes after injection to monitor for signs of orbital compartment syndrome.

The aim of TRAMB procedure is to prevent development of orbital cellulitis in post-operative FESS debridement, reduction of orbital cellulitis who already having orbital cellulitis and to assess the amount of visual improvement with recovery of above mentioned orbital problems and also identifying the associated cause of IFROS.

Visual assessment at the time of admission and then after every dose of TRAMB was done, using Snellen's chart, pin hole and fundoscopy.

Inclusive criteria of IFROS: PNS fungal infection mainly ethmoid sinusitis with orbital cellulitis based on clinical findings, CT findings, MRI findings.

Exclusive criteria of IFROS: Those cases without history of covid infection and with CNS involvement are excluded from this study.

III. Results:

A Total of 300 consecutive cases of , biopsy proven and with radiographic evidence of orbital involvement of Invasive Fungal Rhino-Orbital Sinusitis(IFROS) were evaluated, at a tertiary care hospital, in coastal districts of South India, from April 2021-July 2021.

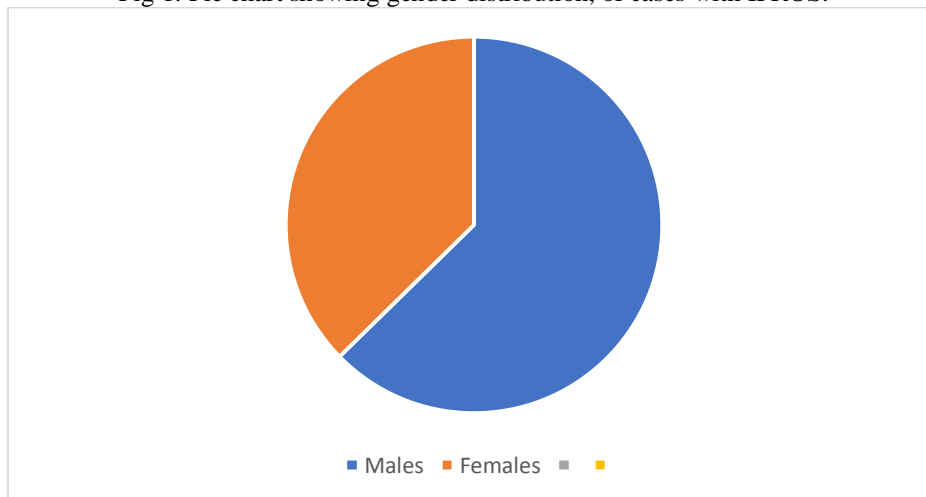
Based on clinical features and radiological findings, only right orbit was involved, in 150 cases and only left orbit in 90 cases. Both the right and left orbits were involved in 60 cases.

A total number of 360 eyes were evaluated.

Gender distribution: Total number of patients: 300.

Number of Males 188 , Number of Females: 112. M:F ratio is 1.3:1.

Fig 1: Pie chart showing gender distribution, of cases with IFROS.



Age Distribution: The youngest Patient was a 27yrs old male and the oldest was 74yrs male. The maximum number of cases were observed in the 4th and 5th decades.

Fig 2: Histogram showing age distribution of IFROS cases.

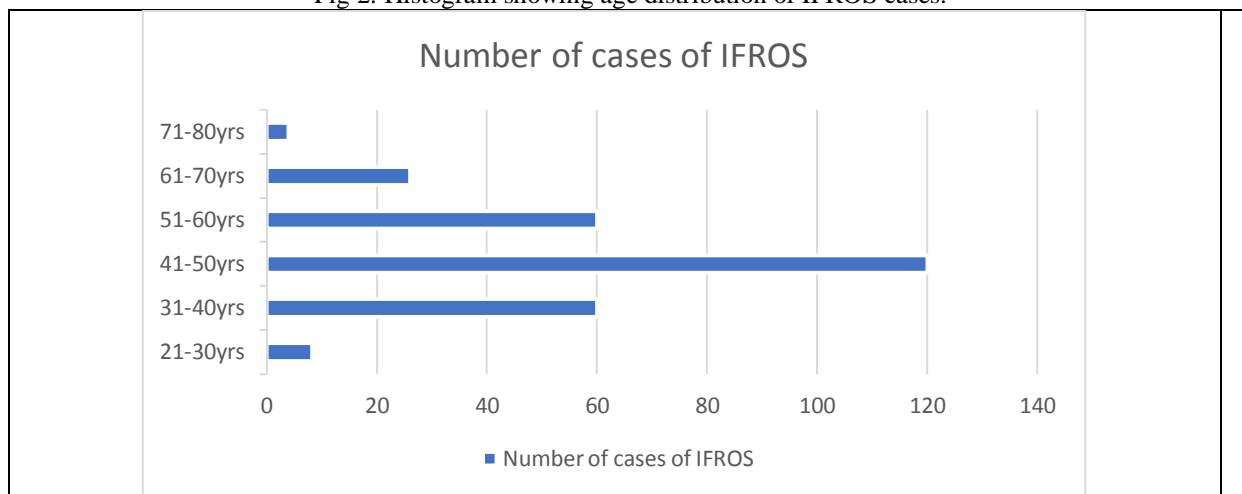


Table 1 showing presenting features in a total of 300 cases with 360 eyes

| Presenting features | Number of eyes | Percentage % |
|---|----------------|--------------|
| Extraocular muscle limitation | 220 | 61% |
| Orbital pain | 320 | 89% |
| Proptosis | 180 | 50% |
| Ptosis | 320 | 89% |
| Conjunctival chemosis | 320 | 89% |
| Central Retinal Venous occlusion (CRVO) | 180 | 50% |

Table 2 showing radiological findings in 360 eyes, at the time of admission.

| Imaging feature | Number of eyes | Percentage % |
|--------------------------|----------------|--------------|
| Orbital cellulitis | 360 | 100% |
| Orbital apex involvement | 220 | 61% |
| Sinus involvement | 360 | 100% |

Table 3 showing Visual acuity in a total of 360 eyes, at the time of admission.

| Visual acuity | Number of eyes | Percentage % |
|-----------------------|----------------|--------------|
| No light perception | 200 | 61 % |
| Light perception only | 80 | 25% |
| *HM | 40 | 11% |
| **CFCF | 10 | 2.7% |
| CF 1m,2m,3m 4m,5m | 10 | 2.7% |
| 6/60 | 10 | 2.7% |
| 6/36 | 10 | 2.7% |
| 6/24 | 05 | 1.4% |
| 6/18 | 05 | 1.4% |
| 6/12 | 05 | 1.4% |
| 6/9 | 05 | 1.4% |
| 6/6 | 20 | 5.5% |

*HM- Hand movements. **CFCF – counting fingers close to face.

Table 4 showing systemic status of total 300 patients.

| Systemic status | Number of cases-Total 300 | % |
|--|---|------|
| Known Diabetic | 150 | 50% |
| De-novo diagnosis of Diabetes, after COVID infection | 150 | 50% |
| Known Hypertensives | 180 | 60% |
| HIV/AIDS | 2 | 0.6% |
| Post renal transplant | 2 | 0.6% |
| Known case of Hepatitis B | 2 | 0.6% |
| Covid vaccination status | 20 cases had taken 1 st dose | 6.6% |

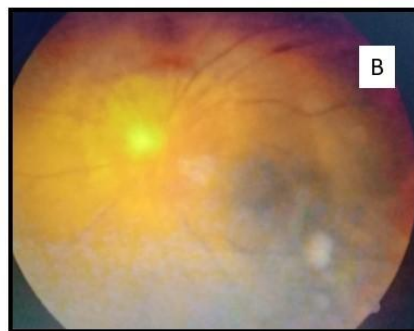


Fig 1: shows clinical picture (A) affecting the right orbit and corresponding fundus(B) findings with CRVO.

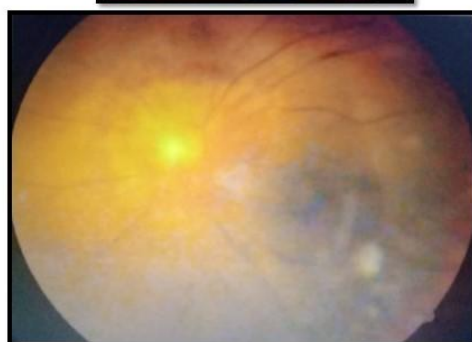


Fig 2: Shows clinical picture who underwent FESS and with left orbit involvement. The fundus is showing CRVO changes.

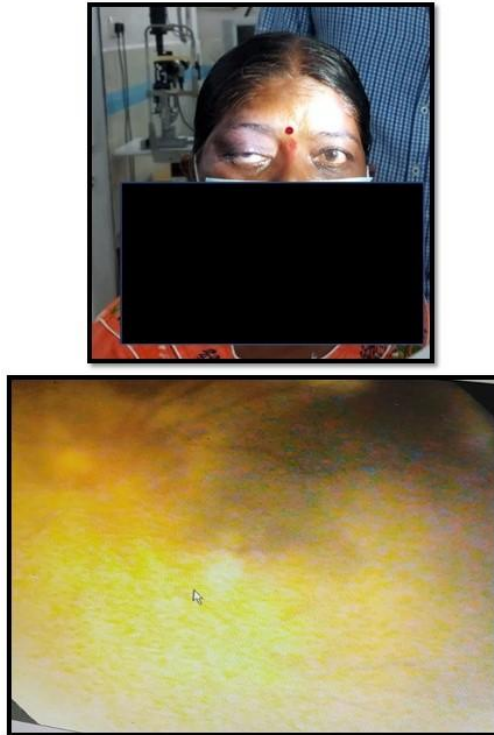


Fig 3: Shows clinical picture with involvement of right orbit with ptosis and corresponding fundus picture with CRVO changes with disc edema.



Fig 4: shows clinical picture with involvement of left orbit with ptosis and corresponding fundus findings with CRVO changes.

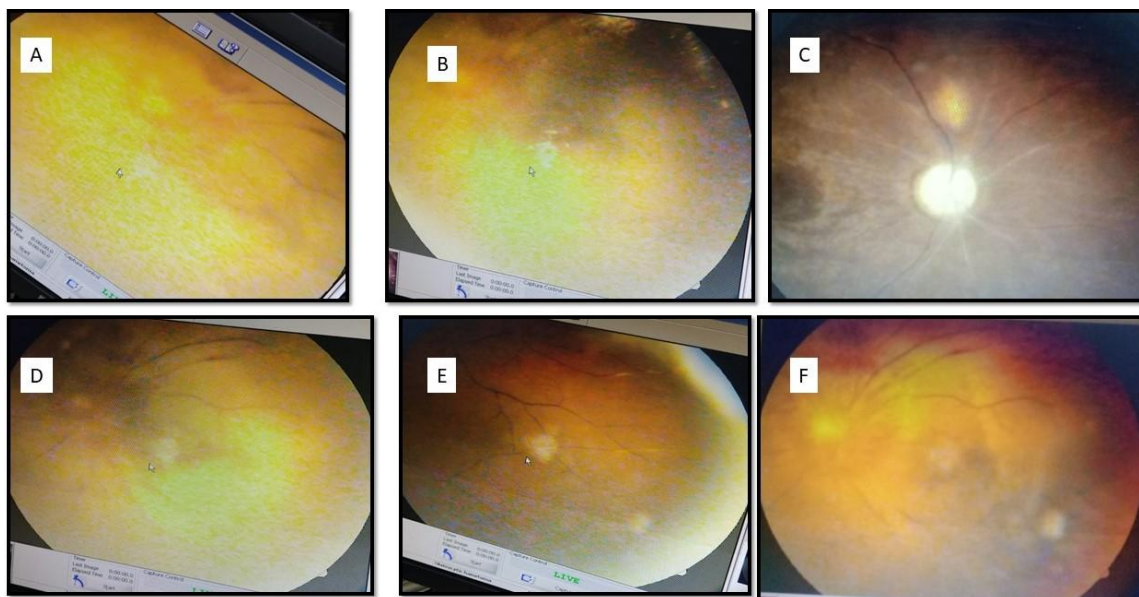


Fig 5: Shows fundus picture of different cases. A, B, D, E, F – shows CRVO changes.
C- shows Optic atrophy.

IV. Discussion:

A total number of 360 eyes (Only right eye/orbit 150 cases, only left eye/orbit in 90 cases and both right and left eyes/orbit in 60 cases), in Post COVID- IFROS are included in the study, conducted at a tertiary care hospital, in coastal district of Andhra Pradesh, INDIA.

Male to Female ratio, was showing slight male predominance, with M:F =1.3:1.

Maximum number of cases were recorded in the 4th and 5th decades of life.

COVID-19 and mucormycosis share risk factors, such as presence of DM, which independently contribute to mortality, but have conflicting management principles. While immune suppression with steroids may be required in moderate to severe COVID-19, the use of steroids and the worsening glycemic control provide an opportunity for mucor to become invasive. Mucor produces keto-reductase as a virulence factor enabling them to grow in the acidic and glucose-rich environment generated in ketoacidotic states^{8,9}.

All the 300 cases, in the present study were Diabetics, with average blood sugar levels of 300mg/dl and nearly 60% of them were known hypertensives.

In a study by Ashraf DC et al¹⁰, the prevalence of diabetes as a cause of immunosuppression was 50% and 40% in the pre-2015 and post-2015 groups, respectively.

In the present study, 0.6% (2 cases) were known HIV cases and another 0.6% were known Hbs Ag cases and 0.6% (2 cases) were post renal transplant cases.

A history of solid organ transplantation was found in 10% of pre-2015 cohort and 13.3% post-2015, in the study by Ashraf DC et al¹⁰.

In this study, the presenting features like headache, facial fullness, conjunctival chemosis, black eschar in nose, Orbital pain, extraocular muscle limitation were most common symptoms, observed in 80-90 % of eyes. Ptosis in 60% of eyes and Proptosis in 20% of eyes was recorded. CRVO changes were noted in 50% of eyes.

In the present study, the radiological findings showed sinus involvement and orbital cellulitis in all the 300 cases(100%). Orbital apex involvement was seen in 61% of the eyes.

The visual acuity of 360 eyes recorded in the present study were, in 61% of eyes, there was no light perception. Light perception only in 25% of eyes and hand movements in 11% of the eyes. CFCF in 2.7% of eyes and CF from 1m,2m,3m,4m,5m was recorded in 2.7% of the eyes.

6/60 visual acuity was noted in 2.7% of the eyes, 6/36 visual acuity in 2.7% of the eyes and 1.4% of the eyes showed 6/24 acuity. Visual acuity of 6/18,6/12 and 6/9 were recorded in 1.4% of cases, each, respectively.

6/6 visual acuity was noted in only 5.5% of eyes.

Moorthy et al¹² reported 18 patients with ROCM with COVID-19 infection. Loss of vision was noted in 67% of patients and 39% underwent orbital exenteration. Mortality was seen in 33%.

Ravani et al¹³ published a series of 31 patients with ROCM following COVID-19 and suggested that the presence of cerebral involvement and a HBA1c value of > 8 were found significant in the prediction of mortality in this subset.

In the present study, TRAMB was done for all 360 eyes, as a globe sparing technique. Kashkouli et al¹⁴ in their series found that survival was not significantly different in patients with and without exenteration.

Exenteration , by itself , may not be associated with improved survival due to end-stage disease at the time of exenteration ¹⁵.

Dave et al ¹¹ study, bivariate regression analysis showed exenteration to be associated with higher mortality although the significance was not maintained on multivariate analysis. This observation was confounded by the possibility that patients with the most severe infection and the highest risk of dying were exenterated. Also Dave et al suggested that, in cases of ROCM involving the sinuses, the orbit along with intracranial extension, orbital exenteration at best may help in reducing the disease load; which by itself cannot be curative.

Patients with IFROS, treated with TRAMB had a lower risk of disfiguring exenteration without an apparent increase in the risk of mortality.

TRAMB is a viable therapeutic option in cases of orbital mucormycosis, where aggressive orbital debridement is not favored and the burden of orbital disease is not substantial.

Transient episodes of orbital inflammation were observed in 30% of eyes, following TRAMB, in this study.

In the present study, less than 5% of the eyes with IFROS, had orbital compartment syndrome, following retrobulbar injection of amphotericin B.

The progression of orbital infection was halted in 70% of the eyes and visual acuity restored with eventual hospital discharge in 20% of eyes, following TRAMB, in this study.

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