International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(RESEARCH ARTICLE)

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Comparison between amphotericin b and posaconazole as consolidation therapy in invasive fungal sinusitis (mucormycosis)

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International Journal of Science and Research Archive, 2024, 11(01), 841–848

Publication history: Received on 29 November 2023; revised on 14 January 2024; accepted on 17 January 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.11.1.0021

Abstract

Aim: To analyse the effects of combination therapy with Injection liposomal Amphotericin B (LAmB) and Tablet Posaconazole in Mucormycosis.

Acute invasive fungal sinusitis is an uncommon disease that often has rapid and destructive clinical progression. Priorly, a disease of the immuno-compromised, Invasive fungal sinusitis is typically associated with patients undergoing chemotherapy, stem cell transplantation as well as in patients with uncontrolled diabetes mellitus and patients using corticosteroids.

Materials and methods: This retrospective observational study was carried after obtaining institutional ethical committee on a total of 40 patients with history of diabetes mellitus, covid positivity, infusion of steroid injections and immuno-compromised were admitted and treated between May 2021 to July 2021.

Results: Any potential combination therapy study under consideration for testing in patients with Mucormycosis should use polyene, as backbone therapy. Injection Amphotericin B remains the only antifungal agent licensed by the US Food and Drug Administration for primary therapy of Mucormycosis.

Tablet Posaconazole reported 90% minimum inhibitory concentrations with Mucorales range from 1 to >=4 microgram/ml. In febrile neutropenic patients or those with mucormycosis,

Conclusion: Mucormycosis is a disease of increasing frequency. It continues to have a higher mortality rate than most other infections, frequently affects young patients.

Keywords: Mucormycosis; Treatment; Diabetes mellitus; Mucorales

1. Introduction

Acute invasive fungal sinusitis is an uncommon disease that often has rapid and destructive clinical progression. Primarily, a disease of the immunocompromised, Invasive fungal sinusitis is typically associated with patients undergoing chemotherapy, stem cell transplantation as well as in patients with uncontrolled diabetes mellitus and patients using corticosteroids or other immunosuppressive therapies (ex: undergone organ transplantation). Amphotericin B and Posaconazole (mold-active agents) has been proven to be effective in Invasive Fungal Sinusitis- IFS (Mucormycosis) according to previous study. It is less commonly described in HIV – infected patients, in whom invasive aspergillosis rather than Mucormycosis is usually described.[3] The estimated mortality of IFS varies markedly, with an

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estimated aggregate mortality of approximately 50% .[5-7] IFS can also have profound effects on malignancy – related survival by delaying or resulting in dose – reduction in chemotherapy regimens.[8]

Limited available interventions as well as slow development of new anti-fungal agents have led to incremental improvements in outcomes.

2. Materials and methods

This retrospective observational study was carried after obtaining institutional ethical committee on a total of 40 patients with history of diabetes mellitus, covid positivity, infusion of steroid injections and immuno-compromised were admitted and treated between May 2021 to July 2021. All were aged between 18-70 years. Radiological investigations including CT scan of Nose and Para-nasal sinuses and Contrast MRI Brain and Nose & PNS were taken to plan the medical interventions and surgical debridement. The data will be collected from in-patient medical records (IP-MRD).The Statistical method used here is Descriptive analysis. The Figures 1-2 showing CT Scan Nose & PNS, MRI Brain and Nose & PNS.

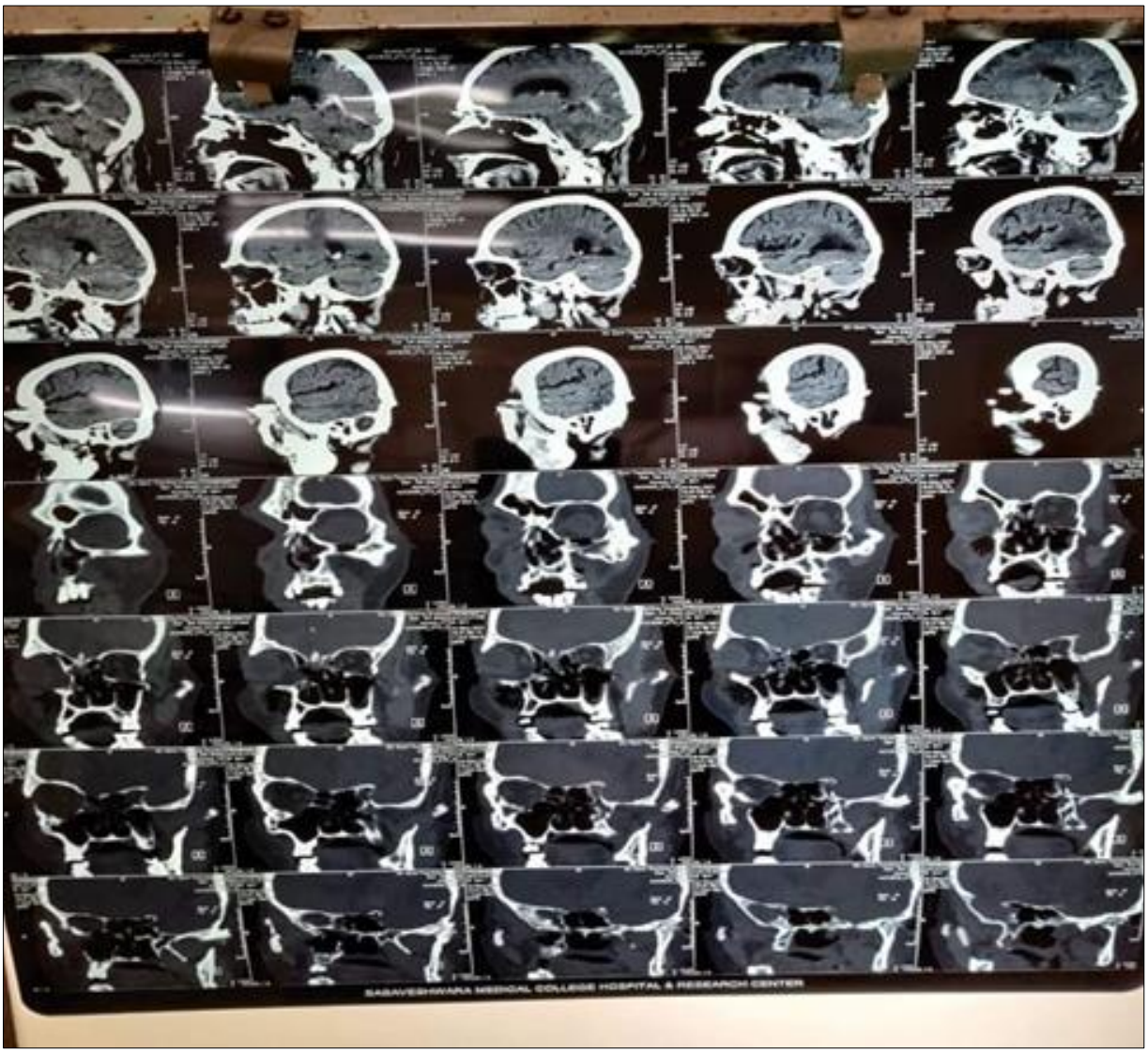
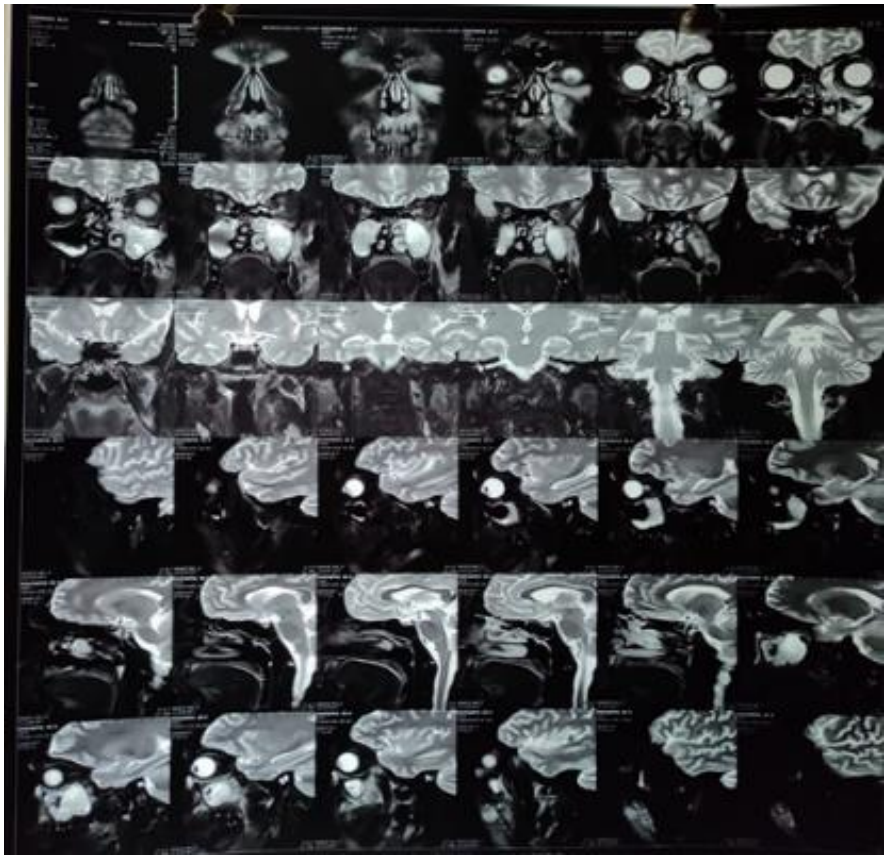
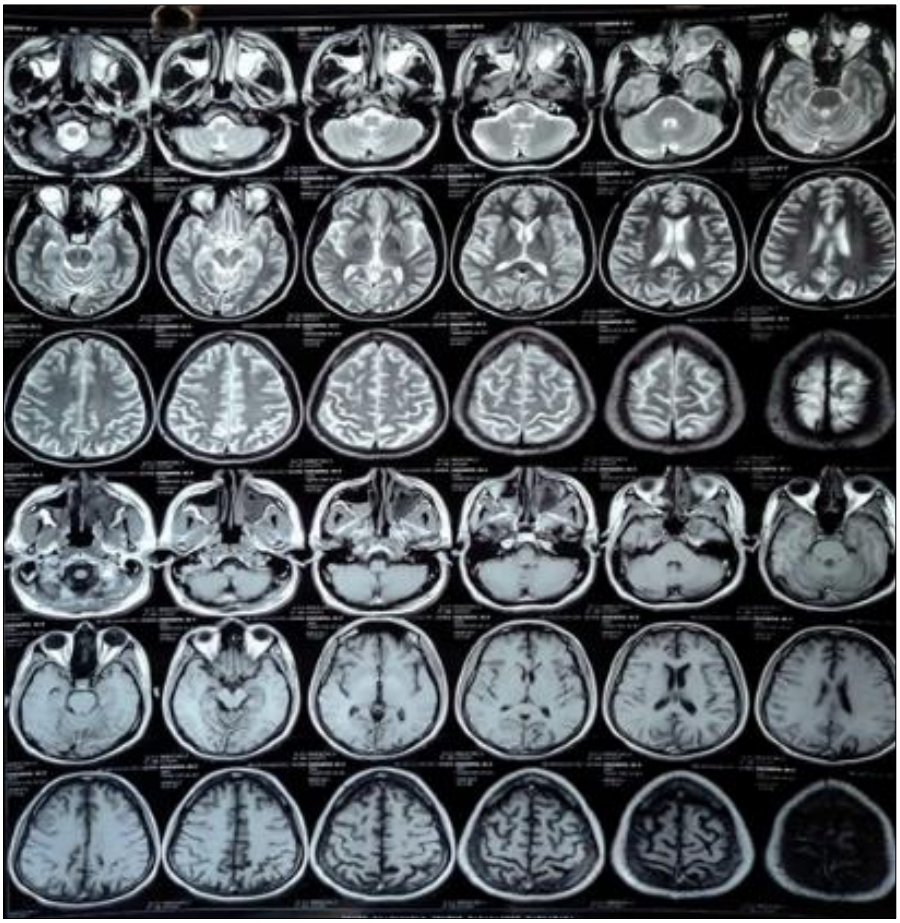


Figure 1 CT Scan Nose & PNS - axial, coronal & sagittal sections with 2mm cuts-opacified left maxillary sinus with hyperdense material & pronounced sinus wall hyperostosis





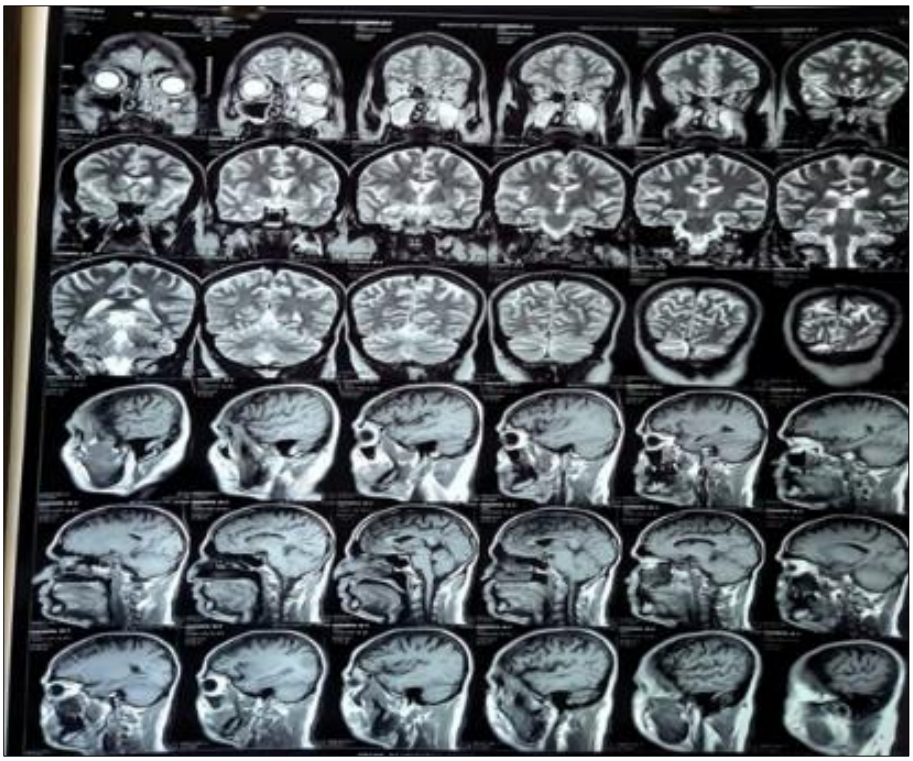


Figure 2 MRI Brain and Nose & PNS- a) Axial, b) Coronal & c) Sagittal sections

(a) Inclusion criteria: 1.Diabetes mellitus patients, 2.RTPCR Confirmed Covid positive patients, 3.Patients hospitalized and receiving systemic IV Steroid injections, 4. 18-70years age group.

(b) Exclusion criteria: 1. <18years age group, 2.Pregnant and lactating women.

3. Results

Any potential combination therapy study under consideration for testing in patients with Mucormycosis should use polyene, as backbone therapy. Injection Amphotericin B remains the only antifungal agent licensed by the US Food and Drug Administration for primary therapy of mucormycosis. However, 2 lipid formulations of Inj.Amphotericin: Amphotericin B lipid complex (ABLC) and LAmB, are licensed for the treatment of invasive mold infections that are refractory to or occur in patients intolerant of LAmB.

LAmB is less nephrotoxic with superior eradication capacity of fungus from the CNS and higher cure rates. Reasonable dose for LAmB would be 5 mg/kg/day, with possible escalation to 10 mg/kg/day in patients with CNS infection.[2-4]

Tablet Posaconazole (new triazole) reported 90% minimum inhibitory concentrations with Mucorales range from 1 to >=4 microgram/ml. In febrile neutropenic patients or those with Mucormycosis, Tablet Posaconasole dosed at 400 mg orally twice daily typically resulted in serum levels <1microgram/ml, with considerable variability, particularly in patients with mucositis and diarrhea. The loading dose on day 1will be 2 x 300 mg IV or oral tablet 2 x 300 mg/day for oral suspension: followed by 4 x 200 mg/day (with food) as second line in Mucormycosis.[4-5]

Therefore, pharmacokinetic & pharmacodynamic data raise concerns about the reliability of achieving adequate in-vivo levels of oral Posaconazole to treat Mucormycosis.[4-5]

The modest existing pre-clinical and clinical data do not support the use of combination therapy, with the possible exception of CNS mucormycosis, where a combination of high dose LAmB and Posaconazole might be considered.[6-10]

The Figures 3-7 showing Pre-operative and Post-operative pictures of Surgical Debridement, Fungal Hyphae-Histologic picture, Tab.Posaconazole and Inj. Amphotericin B.

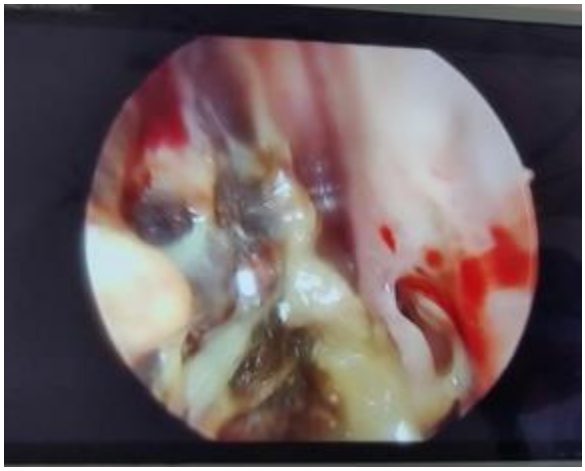


Figure 3 Fungal Ball in maxillary sinus, endoscopic view-Variegated debris with variable consistency and surrounding purulent exudate

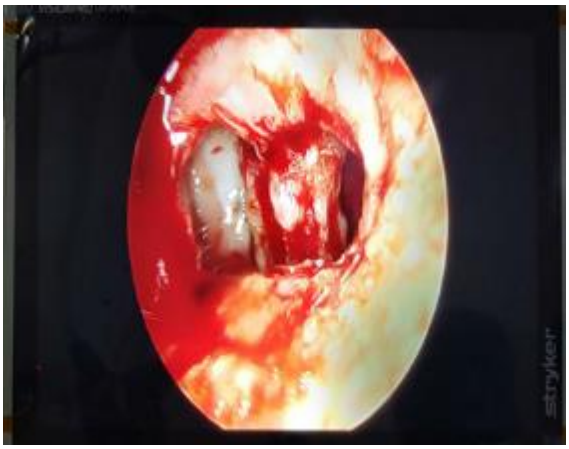


Figure 4 Surgical debridement done, finally reached Sphenoid Sinus

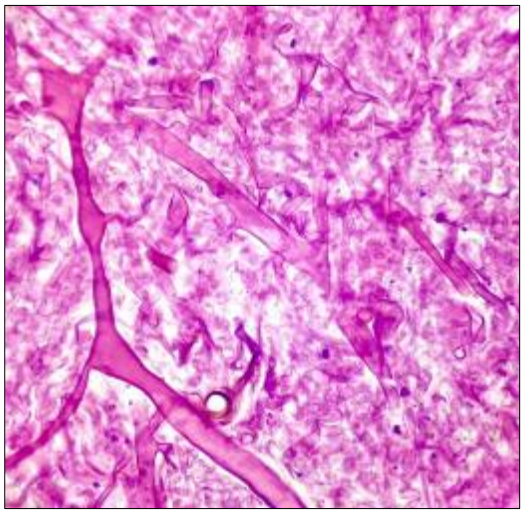


Figure 5 Microscopic picture of Fungal Hyphae-H&E staining, 100 X Magnification

Figure 6 Posaconazole 100mg Tablets Box

Figure 7 Injection Liposomal Amphotericin-B 50mg

4. Discussion

The standard of care in all the cases, have analysed appears to be a combination of surgical debridement and medical intervention. The most commonly used antifungal treatment as first line of therapy for Mucormycosis is injection liposomal Amphotericin B (LAmB).[3-4]

There were three reasons for introducing Posaconazole in a given patient. Firstly, treatment failure demands for a salvage treatment option. Secondly, lipid based Amphotericin B may cause toxic side effects, like nephrotoxicity ex: in patients with long-term uncontrolled diabetes. Thirdly, in successfully treated patients Posaconazole may be used as a step-down to oral medication.[4-5] Since it is a retrospective literature review, the diagnostic criteria used for establishing diagnosis of Mucormycosis varied among publications. In many reports no exact dosages were mentioned. Only a fraction of cases reported the reason for treatment change. In some literatures, they suggests the Posaconazole may be a feasible salvage treatment for mucormycosis and is often used in combination with LAmB formulations[5-6].

The causative organisms are Aspergillus genus and Zygomycetes phylum. Aspergillus sp. are - A.fumigatus, A.niger, A.terreus. Zygomycetes from Mucorales are like – Mucor, Rhizopus, Absidia. Finally, Fusarium sp. The risk factors are poorly controlled DM, chronic CST usage, Iron overload, HIV/AIDS, Stem cell or organ transplant recipients, patients with cancer,[6-8] inhaled cocaine abuse,[8-10] sporadic cases, ketoacidosis due to increased Beta-hydroxy-butaryrate in DKA[11-14] .

The clinical presentations are fever, facial swelling, nasal congestion, facial pain, headache, diplopia, cranial nerve involvement, involvement of nasal cavity, turbinates and facial lesions with necrosis of nasal bridge, necrotic eschars, decreased visual acquity, dysfunction of extraoccular movements, proptosis, photophobia, chemosis, orbital and peri-orbital oedema with cellulitis, loss of smell, ulcerations/ eschars/ ischaemia/ necrosis of oral cavity, gingiva, hard palate, decreased sensation/ paraesthesia over forehead and upper cheek. Then CNS involvement are confusion, seizures, headache, nuchal rigidity. Cutaneous presentation is rare[15-18].

The routine investigation to come for the provisional diagnosis like plain X-ray of Nose and PNS shows air fluid levels with sinusitis. CT scan of Nose & PNS shows sino-nasal mucosal thickening (unilateral) and bony destruction occurs in chronic conditions of the disease. MRI shows necrotic tissues, tissue ischaemia secondary to angio-invasion by fungal organisms, extent of disease by any intracranial or cavernous venous involvement/ invasion into other surrounding structures. This helps to determine appropriateness and extent of surgical excision. Diagnostic nasal endoscopy done and pre-operative & post-operative biopsy specimen sent to HPE and Cytology[19-20].

Fungal Biomarkers have done with (1-3)-B-D-glucan. Later other tests have done like PCR, broncho-alveolar lavage fluid, serum, molecular testing in tissue via PCR, immunohistochemistry, in-situ hybridization[21-22]. In this study the management of this disease goes like adjunctive therapy, reversal of underlying immunosuppression and treatment duration and follow up and outcomes[23-25].

5. Conclusion

Mucormycosis is a disease of increasing frequency. It continues to have a higher mortality rate than most other infections, frequently affects young patients, resulting in devastating impact on families and even in survivors. Hence, there is a great need for new therapies for these infections. One should recognize the critical need for combination-therapy studies for this infection and public good that could result from such studies.

Further studies are required to know about the comprehensive details on microbiological findings, exact treatment dose, reason for treatment choice, and definition of treatment response.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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