(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 6, Page No: 753-756
November-December 2021

IJMSCR

Outcome of Hyperbaric Oxygen Therapy in Post-Covid Invasive Mucormycosis

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Keywords: NIL

Introduction

Hyperbaric Oxygen therapy is an established modality of treatment in decompression injury, carbon monoxide poisoning, gas embolism etc. It is also used as an adjunctive therapy in other indications such as Refractory osteomyelitis, radiation and ischemic injuries. (1)

A recent spike in the incidence of mucormycosis has been noticed in India, coinciding with the COVID-19 pandemic, which has been found to be associated with high mortality(upto 44%) and morbidity(2) (3) The treatment options available in the current scenario are surgical debridement and medical management with Mold active azoles(Posaconazole or Isavuconazole) and Amphotericin B. The current treatment protocols are lengthy, associated with significant toxicities and financial burden.

There have been anecdotal reports favouring the use of HBOT as an adjunctive therapy in Invasive Mucormycosis.(4)

Here we are presenting to you a case compilation of 10 patients with Invasive Post COVID -19 Mucormycosis ,who had clinical or radiological worsening on the standard treatment protocol. These patients were offered HBOT as an adjunct therapy and they were evaluated retrospectively for 30 day mortality and disease progression.

Case Series:

We retrospectively reviewed patients with Post COVID-19 mucormycosis admitted at our centre under the departments of Infectious Diseases and Otorhinolaryngology and Geriatrics, who received HBOT as an adjunctive therapy, between August 2021 to September 2021.

These patients had histopathologically or microbiologically proven Post COVID-19 invasive mucormycosis. The patients enrolled were the ones who had features suggestive of invasive fungal infection occurring either concomitantly or within 3 months of their presentation with COVID-19. Patients who were found to have signs and symptoms of disease progression after 4 week of adequate treatment with antifungals (intravenous and/or oral) and surgical debridement were offered HBOT at our centre as an investigational therapy after taking informed consent for the same.

Disease progression was defined as clinical deterioration, endoscopic evidence of persistent disease or radiological worsening.

Patients who had middle ear disease, Pneumothorax, Claustrophobia, Sepsis, restrictive airway disease, those on chemotherapy or who did not give consent for the HBOT, were not included.

Patients were offered 1 to 2 weeks of HBOT consisting of once a day session of 60-90 minutes duration.

The pressure settings were incrementally raised from 1.6ATA to target ATA of 2.0 to 2.5 depending on tolerance.

The patients were then followed up for any clinical worsening or mortality over a minimum period of 30 days.

Demographics showed that 80% of the study participants were male with a mean age of 51.8 years and a median age of 55 years. Duration between date of onset of COVID-19 and development of symptoms suggestive of mucormycosis was varied with 10% reporting concomitantly, 40% presenting within 2 weeks, another 40% between 2-4 weeks and 10% after 4 weeks.

The major distinguishing characteristics are mentioned in the Table -1

Majority of the patients presented with Rhino-orbital involvement (8 out of 10 patients).

All of them were treated with Amphotericin B. The medical management of these patients consisted of Amphotericin B as initial injectable therapy followed by suppressive therapy with one of the mold active azoles. Combination therapy of Amphotericin B with Azoles is not indicated in the initial stages but half (50%) of our patients received them because of unavoidable circumstances. This aberration was due to the inconsistent availability of amphotericin B and anti mold azoles at the beginning of the second wave of COVID-19 in the country.

All subjects received a minimum of 21 days of Liposomal amphotericin B (5mg/kg) and at least 8 weeks of Posaconazole/isavuconazole. Patients with mucormycosis were routinely initiated on antifungal regimen for 4-6 weeks and if anyone showed signs of worsening as described above, they were offered HBOT as an adjunctive treatment. There were no changes in the routine treatment protocol (including debridement/ antifungals used) even after HBOT initiation. The time duration and settings which were offered to each patient are mentioned in the Table -2

The mean of the minutes of HBOT provided was 789 minutes and the mean ATA was 2.28.

There was no mortality observed after 30 days post HBOT in our cohort. Only one patient had radiological progression requiring debridement, while on HBOT and was followed upto 2 more months with no further features suggestive of progression.

Discussion

Invasive zygomycosis, also called mucormycosis, is the third most common invasive fungal disease worldwide [(1)] It is usually seen in immunocompromised or severely ill patients and is associated with a high mortality rate.

The pathological hallmark of this disease is vascular invasion with marked hemorrhagic necrosis. Mucormycosis has different modes of anatomic presentation like rhinocerebral, pulmonary, disseminated, gastrointestinal, cutaneous and uncommon presentations(5)

The most common predisposing factors, based on available data are haematological malignancies, stem cell transplantation, prolonged and severe neutropenia, poorly controlled diabetes mellitus with or without diabetic ketoacidosis, iron overload, major trauma, prolonged use of corticosteroids, illicit intravenous drug use, neonatal prematurity and malnourishment.(5) Our study cohort also had diabetes mellitus and prolonged use of corticosteroids as the predominant predisposing factors. Correlation between the COVID and Mucormycosis still remains unanswered, opening up an opportunity to further study molecular and genetic links between the two.

The use of antifungal agents like Amphotericin B, Posaconazole, isavuconazole, accompanied by frequent surgical debridement remain the cornerstone of management. As mortality rates with standard treatment regimens were significantly high, adjunctive treatment options were proposed, Hyperbaric Oxygen Therapy being one of them. HBOT has been looked up as the adjunctive therapy for Zygomycosis since 1988, still the clinical application of HBOT lacks the substantial evidence.(6)

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Hyperbaric oxygen therapy involves inhaling 100% oxygen for a certain time at a certain pressure. Primary mechanism of action is by reduction in oedema by vasoconstriction and decrease in leukocyte chemotaxis and adhesion. It also reduces ischemic reperfusion damage and formation of the inflammatory mediators. (7)

HBOT inhibits fungal growth at pressures more than 10 Atmosphere absolute, as seen in the in vitro studies. (8). It corrects the lactic acidosis at the site and facilitates the action of antifungal drugs like amphotericin B. (9)

In a murine model study it was seen that the addition of HBOT to amphotericin did show survival benefit when compared to no treatment at all, they concluded that there were no harmful effects of the hyperbaric therapy noted although the positive effects were not substantial.(10)

John BV et al found that using HBOT as an adjunct can increase the survival by 94% in diabetic patients , although it was found less useful in case of the patients with haematological malignancies with or without transplant.(4)

Hence, by means of a retrospective study involving 10 patients diagnosed with post-COVID- 19 Invasive Zygomycosis, we attempted to look at the outcomes of HBOT. 9 out of 10 patients were diabetic and all of them received steroids for the management of COVID-19.

There was no mortality noted at the end of thirty days. 50% of the patients, who had a time interval of 2 months post HBOT, didn't show any signs of disease progression or relapse. Our findings were consistent with the anecdotal case reports that have been documented in the past.

The sample size of our study was small and we still cannot comment on long term outcomes of the cohort. There were no drop-outs and none of the patients experienced any adverse outcomes secondary to HBOT. These patients are under close follow up and long-term outcomes are being studied.

Mucormycosis is a serious invasive mycosis, which can lead to increased mortality and morbidity. The treatment options available are limited and they have their own limitations, therefore there is a need to look for more modalities to address Zygomycosis. Evidence regarding HBOT is few and far between, but encouraging results have been noted in the past, hence can be explored more for its benefits as one of the treatment options.

Acknowledgment

Dr. Ashok BC (Department of Plastic surgery, Manipal Hospitals Bengaluru), Dr. Srikanth V(Department of Plastic surgery, Manipal Hospitals Bengaluru), Dr.Anantheswar Y.N(Department of Plastic surgery, Manipal Hospitals Bengaluru), Dr.Ranjitha (Department of Microbiology, Manipal Hospitals Bengaluru),Dr.Bhavna (Department of Microbiology, Manipal Hospitals Bengaluru),Dr.Sushmitha (Department of Pathology , Manipal Hospital Bengaluru), Dr. Adithya Hegde(Department of Endocrinology , Manipal Hospital Bengaluru), Dr. Adarsh KS(Department of Endocrinology , Manipal Hospital Bengaluru)

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TABLE -1

Characterstics	**(n=10)**
1. Predisposing factors	
Steroids	100% (10/10)
Oxygen	50%(5/10)
Tocilizumab	10%(1/10)
Diabetes	90%(9/10)
Other immunosuppresants	None
2. Time of onset of Invasive Mucormycosis	
Concomitant	10%(1/10)
<2 weeks	40%(4/10)
2-4weeks	40%(4/10)
>4 weeks	10%(1/10)
3. Type of involvement	
Rhino-orbital	80%(8/10)
Rhino-cerebral	10%(1/10)
Rhino-orbito-cerebral	10%(1/10)
4. Treatment received	
Amphotericin plus mold active azole*	50%(5/10)
Amphotericin followed by mold active azole*	50%(5/10)

TABLE-2

Serial Number One	**HBOT-1/*HBOT2	TOTAL SITTINGS	Average minutes	Targeted #ATA
Patient 1	9+1	10	630	2.0
Patient 2	1+9	10	870	2.0
Patient 3	1+9	10	870	2.0
Patient 4	1+9	10	870	2.5
Patient 5	1+9	10	870	2.5
Patient 6	1+8	09	780	2.5
Patient 7	9+1	10	630	2.3
Patient 8	8+5	13	930	2.0
Patient 9	2+5	7	570	2.5
Patient 10	1+9	10	870	2.5

****HBOT-1 implies 60 minutes session**
***HBOT-2 implies 90 minutes session**
#ATA- Atmospheric Absolute

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