

Use of Hyperbaric Oxygen in The Management of Rhino-Orbital-Cerebral Mucormycosis (Comparative Study)

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ABSTRACT

Introduction: Rhino-orbital-cerebral mucormycosis (ROCM) is considered a mortal disease induced by fungi. Mucormycosis is mostly found in patients suffering from diabetes mellitus, who performed organ transplantation, or in malignancy due to the immunocompromised state of these patients. Surgical intervention must be done, and better to do aggressive debridement for all involved tissues to attack the fungal load. Adjuvant therapies can be used, and among which is hyperbaric oxygen treatment (HBOT). **Aim:** This study aims to prove the effectiveness of HBOT in cases of Rhino-orbital-cerebral mucormycosis (ROCM) and whether it affects the outcome.

Patients and Methods: The present study involved twelve patients presented by ROCM in the ENT Department, at Ain Shams University Hospital. Half of them received HBO in the hyperbaric chamber, while the other half were not treated with HBO. **Results:** Our results revealed the effectiveness of HBO as an adjunct therapy improving the outcome when it was added to both surgical debridement and antifungal therapy.

Conclusion: HBOT can act as an adjunct therapy together with antifungal treatment and surgical debridement to improve the outcome in the treatment of ROCM.

Keywords: Hyperbaric oxygen, Rhino-orbital-cerebral mucormycosis (ROCM), Invasive fungal sinusitis.

INTRODUCTION

Rhino-orbital-cerebral mucormycosis (ROCM) is considered a mortal disease induced by fungi. Mucormycosis is mostly found in patients suffering from diabetes mellitus, who performed organ transplantation, or in malignancy due to the immunocompromised state of these patients^{1,2}. The incidence of mucormycosis appears to be increasing, especially during the covid era.

ROCM is generally attributed to *Aspergillus* or *Mucor* in immunocompromised patients, also related to neutrophil dysfunction proved by evident neutropenia or also due to diabetes mellitus. The treatment plan generally included surgical debridement and drainage accompanied by systemic antifungal drugs³.

Surgical intervention must be done, and better to do aggressive debridement for all involved tissues to attack the fungal load. Adjuvant therapies can be used, and among which are hyperbaric oxygen treatment (HBOT)⁴.

Previous studies stated that 100% hyperbaric oxygen at 1-3 atm. has a fungistatic effect, improves tissue hypoxia, enhances oxygen-dependent mechanisms responsible for pathogen killing, and decreases tissue acidosis⁵. Oxygen higher than 1 ATA increases the production of reactive oxygen-free radicals. This has an antimicrobial impact, particularly in anaerobic infections. In addition, the oxygen free radicals have evident bactericidal effects^{6,7}.

PATIENTS AND METHODS

A case control study involved twelve patients presented by ROCM in the ENT Department, at Ain Shams

University Hospitals during the period from January 2022 and June 2022. Half of them received HBO in the hyperbaric chamber, while the other half were not treated with HBO. Precise history was taken including age and gender; active disease status; as well as past history.

They were examined to assess clinical improvement. Follow-up investigations included laboratory serum inflammatory markers, and computed tomography (CT) scans.

• *Hyperbaric oxygen therapy*

Cases treated in a hyperbaric chamber underwent a variable number of 90-minute sessions on continuous weekdays. Sessions were conducted at a pressure of 243.1 kPa (2.4 atmospheres absolute) while breathing 100 percent oxygen.

Throughout HBOT, cases continued antifungal with or without surgical debridement.

Ethical approval:

The current study protocol was approved from Ain Shams University Faculty of Medicine Research Ethics Committee (REC) FWA 00017585. Ethics guidelines for human experimentation by the World Medical Association's Helsinki Declaration were adhered to. Informed consent was taken from each patient.

Statistical methods

Data were analyzed utilizing IBM© SPSS© Statistics version 26 (IBM© Corp., Armonk, NY). Comparison finalized utilizing the Pearson chi-squared

test or Fisher's exact test. The time-to-event analysis is performed employing the Kaplan-Meier approach.

P-values less than 0.05 are statistically significant.

RESULTS

These results revealed the effectiveness of HBO as an adjunct therapy improving the outcome when it was added to surgical debridement and antifungal therapy from 66% to 83% and decreasing the death rate from 33% to 17%. The P-value for the effectiveness of HBOT is < 0.001.

Details of cases were presented in (Table1):

Patient 1

A 53-year-old male with known B-cell lymphoma developed left-sided partial vision loss, and severe ocular pain, associated with proptosis. Brain MRI and orbital CT showed sphenoid and ethmoidal sinuses involvement with intraorbital invasion and cavernous sinus thrombosis. Endonasal endoscopy was done, and a biopsy was taken, which revealed mucormycosis (*Mucor spp* and *Aspergillus fumigates*).

The patient obtained a debridement operation and received one month of antifungal treatment. And started HBOT after 5 days from operation. After 10 sessions of HBOT, marked improvement was detected.

Patient 2

A 30-year-old female with uncontrolled type I diabetes mellitus appeared with right-sided hypoesthesia, purulent discharge, and facial pain from the right nostril for two weeks duration.

MRI was done and revealed affection of paranasal sinuses with cavernous and ocular sinus invasion on the right side. She underwent emergency surgery consisting of endoscopic ethmoidectomy, right maxillary sinus antrostomy, and debridement. She received orbital exenteration. Three months of antibiotics and antifungal medications were administered to her. The infection-free status of the patient was attained after 40 HBOT sessions.

Patient 3

A 20-year-old male with a previously diagnosed T-cell lymphoma reported with left-sided ophthalmoplegia and proptosis. Later, he necessitated left ocular exenteration after undergoing endoscopic sinus surgery with brain abscess drainage. *Rhizopus spp.* was found from a biopsy taken during the endoscopic intervention.

He received five sessions of HBOT and was not able to complete medication as set due to side effects that occurred (nausea, vomiting, and generalized discomfort). He remained on amphotericin B for ROCM treatment. No response to treatment ended in death.

Patient 4

A 50-year-old female with uncontrolled type I diabetes mellitus followed by 4 week's history of left ocular

swelling, pain, and ptosis. MRI was done and revealed ethmoid and sphenoid paranasal sinuses and ocular involvement. Gave history of excess solumedrol usage during previous covid treatment.

She underwent emergency endoscopic sinonasal ethmoidectomy. Sphenoidotomy and maxillary sinus antrostomy on the left side. She was administered antibiotics and antifungal medicine for three months. The patient received twelve sessions of HBOT. After which a complete cure is achieved.

Patient 5

A 65-year-old male post covid with a history of excess solumedrol usage. Presented with 2 weeks history of right ocular swelling, pain, and ptosis. MRI showed diffuse infiltrate originating from the ethmoid and sphenoid paranasal sinuses.

She underwent surgery with sinonasal endoscopic ethmoidectomy. sphenoidotomy and right maxillary sinus antrostomy. She was medicated with antibiotics and antifungal treatment for a two-months duration. The case did 35 sessions of HBOT. After which a complete cure is achieved.

Patient 6

A 35-year-old male with a past history of leukemia followed by rapid onset of right-sided ophthalmoplegia, with proptosis. MRI showed the affection of ethmoid and sphenoid paranasal sinuses with ocular involvement and cavernous sinus thrombosis. Operations were done including extensive debridement accompanied by exenteration.

After referral for HBOT, the patient received 20 sessions. The patient continued on amphotericin B for ROCM treatment. The arrest of disease progression was achieved.

Patient 7

A 50-year-old male with uncontrolled type II diabetes mellitus presented with left ocular swelling, pain, and ptosis with palatal necrosis for 2 weeks duration. MRI showed maxillary ethmoid and sphenoid paranasal sinuses.

She underwent emergency endoscopic sinonasal ethmoidectomy. Sphenoidotomy and maxillary sinus antrostomy on the left side. A one-month course of antifungal medicine was administered to her. Patient healed.

Patient 8

A 55-year-old female with a history of chronic kidney disease. Followed by a 2-week history of right-sided facial pain, swelling, and ptosis. MRI revealed a diffuse affection of ethmoid and maxillary paranasal sinuses. She underwent emergency surgery with endoscopic sinonasal ethmoidectomy and antrostomy. She was given antifungal medication for 5 weeks till improvement.

Patient 9

A 60-year-old male with a history of previous covid illness. Followed by 5 days history of right-sided facial pain, swelling, ptosis, and palatal necrosis. MRI showed ethmoid and maxillary paranasal sinusitis.

She underwent emergency surgery with endoscopic sinonasal ethmoidectomy and right maxillary sinus antrostomy. She was given antifungal medication for 6 weeks. Patient improved.

Patient 10

A 30-year-old male with a past history of leukemia expressed rapid onset of left-sided ophthalmoplegia, with proptosis. MRI revealed ethmoid and sphenoid paranasal sinuses affection with ocular involvement and cavernous sinus thrombosis. Operations were done including extensive debridement accompanied by exenteration. He remained on amphotericin B for ROCM treatment for 2 months which ended with a partial cure of the disease.

Patient 11

A 25-year-old male with a past history of leukemia, existed with rapid onset of right-sided ophthalmoplegia, with proptosis. MRI showed the ethmoid and sphenoid paranasal sinuses affection with ocular involvement and cavernous sinus thrombosis. Operations were done including extensive debridement accompanied by exenteration. The patient remained on amphotericin B for ROCM treatment for 1 month. Deterioration of condition leading to death.

Patient 12

A 22-year-old female with known T-cell lymphoma presented with right-sided ophthalmoplegia, with proptosis. He underwent an operation for the sinuses and was followed later by left ocular exenteration. The patient remained on amphotericin B for ROCM treatment for 1 month, but no response to treatment, and ended in death.

Table 1: Details of cases

Age	Sex	Comorbidities	Extent of disease	Surgery	Treatment	HBO	Fate
53	M	B cell lymphoma	Lt eye affection, ethmoid, sphenoid, cavernous sinus th.	Endoscopic debridement	Antifungal 1m	10 sessions	improved
30	F	DM 1	Right Ocular affection. Cavernous sinus th.	Endoscopic debridement and exenteration	Antifungal 3m	40 sessions	Improved
20	M	T cell lymphoma	Left eye affection, brain abscess	Endoscopic debridement and exenteration	Antifungal 1m	5 sessions	Death
50	F	DM 1	Left eye affection, ethmoid, sphenoid	Endoscopic debridement and exenteration	Antifungal 3m	12 sessions	Improved
65	M	Post covid	right eye affection, ethmoid, sphenoid	Endoscopic debridement	Antifungal 2m	35 sessions	Improved
35	M	Leukemia	Right ethmoid, cavernous sinus th.	Endoscopic debridement and exenteration	Antifungal 2m	20 sessions	Arrest of disease
50	M	DM2	Ethmoid sinus, palatal necrosis	Endoscopic debridement	Antifungal 1m	-----	Improved
55	F	Chronic kidney disease	Maxillary, ethmoid sinusitis	Endoscopic debridement	Antifungal 5w	-----	Improved
60	M	Post covid	Ethmoid sinusitis, palatal necrosis	Endoscopic debridement	Antifungal 3w	-----	Improved
30	M	Leukemia	Left ethmoid, sphenoid sinus	Endoscopic debridement	Antifungal 2m	-----	Partial cure
25	M	Leukemia	Right ethmoid, cavernous sinus th.	Endoscopic debridement and exenteration	Antifungal 1m	-----	death
22	F	Lymphoma	Right ethmoid. Cavernous sinus th.	Endoscopic debridement and exenteration	Antifungal 1m	-----	death

DISCUSSION

Recent research showed that the incidence of fungal sinusitis is believed to have increased. This is mostly owing to greater knowledge, antibiotic overuse, and immunosuppressant medication use⁸.

Other treatment modalities are needed to control this disease's mortality and morbidity. Depending on the aforementioned pathophysiological processes, hyperbaric oxygen (HBO) was proposed as a potential adjuvant therapy. HBO can reduce tissue hypoxia, restore oxygen required for the respiratory granulocyte burst, enhance fibroblast function, reduce tissue lactic acidosis, and boost the oxygen reserve required for the oxidative processes of Amphotericin-B. (AMB). In vitro investigations also demonstrated that high oxygen pressure produces fungistatic and fungicidal impacts⁹.

Price and Stevens added HBO to the therapeutic protocol of a patient with rhino-orbitocerebral mucormycosis ROCM. They noted that before HBO therapy, infected tissue was infested by large amounts of fungi while following HBO, tissue samples showed bacterial contaminants growth only and no fungi¹⁰.

Another large study of 145 patients was done by **Yohai et al.** treated with only amphotericin B and surgical debridement, and the study added another 6 cases treated by adding HBOT, with favorable results that 5 of the 6 patients survived (83%); this seems statistically significant despite the tiny number of patients compared with 87 patients (60%) survived after receiving traditional treatments only⁵. In favor of our findings, **Knipping et al.** proved the role of HBO as they stated that after surgical debridement and medical therapy alone, the disease recurred, while after adding HBO, the patients became free for 2 years during the follow-up period¹¹. In a retrospective study by **Segal et al.** a review of 14 cases treated by adding HBOT in their protocol of treatment showed neutral results, 7 patients survived (50%) and 7 patients died¹².

Another retrospective study involved 12 patients done by **Colon-Acevedo et al.**

Patients were managed by surgical debridement followed by medical treatment by local and systemic Amphotericin B while only one patient treated with HBO, showed a result of a 50% survival rate to a 50% mortality rate¹³.

In the study by **Iharco et al.**, they used Isavuconazole as a salvage therapy with hyperbaric oxygen, for a total of 20 sessions, accomplishing completely good findings¹⁴.

The individual was discharged after eight months, maintained on oral Isavuconazole 200mg/day, and was re-validated at three and six months with no indication of infection progression. The HBO treatment was complicated with the right

middle ear's barotrauma, which needed transtympanic drainage.

In the study done by **Mitbaa et al.** medical and surgical treatment were used with hyperbaric oxygen therapy (HBOT). Patients received 5 sessions per week. The evolution was favorable with no recurrence during 2 years of follow-up¹⁵.

Despite the small number of published articles that provide the efficacy of hyperbaric oxygen in invasive fungal sinusitis medication, still, the optimal technique has yet to be identified.

In the present study, results indicate statically significance that the usage of HBOT as adjunctive therapy for ROCM patients improves the death rate from 33% to 17% with P-value significance for the effectiveness of HBOT being < 0.001. It has a great role in decreasing morbidity for many reasons, as it improves wound healing and angiogenesis, eliminates certain anaerobes, inhibits growth pseudomonas, antitoxin effect, activates neutrophil-mediated bacterial killing mechanisms, decreases leucocytic adhesion, stops free radicals' release which induces cellular deterioration and vasoconstriction. While its side effects and complications are relatively minor, Hyperbaric oxygen therapy (HBOT) is generally considered a relatively safe treatment for multiple circumstances.

CONCLUSION

Hyperbaric oxygen (HBOT) can act as adjunct therapy with antifungal therapy and surgical debridement to improve the outcome of treating ROCM. And decreases the incidence of death in these critical cases. It is advisable to add this modality of treatment in ROCM cases treatment.

Conflict of Interest and financial sponsorship:

The authors have no conflict of interest to disclose.

The authors have no financial sponsorship to disclose.

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