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Anesthesia Management of COVID-19 associated Rhino-Orbito-Cerebral Mucormycosis: A Prospective Observational Study

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ABSTRACT

Background: Fungal infections (mucormycosis) have been reported as co-infection as well as opportunistic infection during and after COVID-19 (Coronavirus disease), involving the paranasal air sinuses with a high risk of morbidity and mortality. Considering the ongoing situation of COVID-19 associated with mucormycosis, we presented our experience of 110 patients being, or having previously been COVID -19 positive. **Methods**: This study included 110 patients in which surgical resection was done for Rhino-orbito-cerebral mucormycosis (ROCM) under general anesthesia and observed for 30 days postoperatively. **Results**: This study included 79 male patients with the majority of 51-60 years of age group (31.81%). Most common comorbidities observed in study were diabetes mellitus (77.27 %) followed by hypertension (39.09 %) & ischemic Heart Disease (9.09 %). Majority patients had received steroids (80 %) as a part of covid-19 treatment. All patients were receiving Amphotericin B at the time of surgery. On operative table extubation was possible in 80 % of the cases while others required average ICU stay (9.83 $\pm$ 7.33 days). Inotropic support was required in 20 % of patients. Majority patients were discharged successfully (85.45 %), while 10.91 % had mortality. On 30 days follow-up frontal Sinus Abscess (6.36 %) & maggots in maxilla and sphenoid (0.91 %) were noted. **Conclusion**: Corticosteroids and DM are the most important predisposing factors in the development of COVID-19-associated ROCM. Perioperative anesthesia care plays an important role towards management and outcome of ROC mucormycosis. Difficult intubation is anticipated due to fungal debris and supraglottic edema in the oropharynx of the patient.

KEYWORDS: anesthesia management, COVID-19, mucormycosis, postoperative outcome, perioperative care

INTRODUCTION

In recent times, fungal infections have emerged as significant concerns, both as co-infections and opportunistic infections during and after the course of COVID-19 (Coronavirus disease). These infections affect various anatomical sites such as the paranasal air sinuses, eyes, lungs, and brain. [1–3] Among these, mucormycosis stands out as a particularly acute, fulminant, and rapidly progressive opportunistic fungal infection, primarily caused by angio-invasive fungi belonging to the family Mucoraceae. [4]

Successful management of mucormycosis hinges upon adherence to key principles, including early diagnosis, treatment of underlying predisposing factors, timely surgical debridement of necrotic tissue, and administration of appropriate antifungal therapy. [5] Surgical debridement is often indicated, especially in the presence of predisposing factors like immunodeficiency, diabetes mellitus, and multiple organ failure, as well as in cases requiring urgent intervention due to conditions such as sepsis. [6]

Multiple factors including post-COVID-19 systemic effects like residual pulmonary dysfunction, adrenal suppression, myocardial dysfunction, difficult airway due to fungal debris and adverse effects of amphotericin B, can alter the anaesthetic outcome in these patients. In particular, airway management of the patients is of paramount importance since the fungal debris in the oropharyngeal region and supraglottic oedema lead to difficult ventilation and endotracheal intubation. [7]

Considering the ongoing situation of COVID-19 associated mucormycosis, it was important to do a study to evaluate perioperative anesthetic management of COVID-19 associated rhino-orbito-cerebral (ROC) mucormycosis undergoing endoscopic surgical debridement. Here, we presented our experience of 110 cases of mucormycosis seen over just

6 months, with these patients being, or having previously COVID-19 positive.

MATERIAL AND METHODS

Study Design and Setting:

This was a single-centre, prospective, observational study conducted over a period of 6 months (March 2021 to October 2021) at Dr SCGMC Nanded, following approval from the Institutional Review Board and the Human Research Ethics Committee. This study is part of the trial registered with the Clinical Trial Registry India (CTRI/2022/01/039622). **Participants:** A total of 110 patients undergoing surgical debridement for rhino-orbito-cerebral (ROC) mucormycosis were enrolled in the study after obtaining written informed consent. Patients were selected using purposive sampling methods.

- **Inclusion Criteria:** All patients scheduled for emergency or elective surgical resection of ROC mucormycosis were included in the study.
- **Exclusion Criteria:** Patients were excluded if they refused to participate or had severe coagulopathy.

Data Collection:

COVID-19 status was confirmed using reverse transcriptase polymerase chain reaction (RT-PCR) or Rapid Antigen Test (RAT) before surgery. Written informed consent was obtained from each patient.

Anesthesia Management:

All patients adhered to ASA fasting guidelines and were confirmed to be nil by mouth. General anaesthesia was administered based on ASA-PS risk stratification. Difficult intubation equipment was prepared for all cases.

Procedure:

Anesthesia induction included intravenous (IV) etomidate (0.2 mg/kg) or IV propofol (1-2 mg/kg) and IV succinylcholine (2 mg/kg). Pre-oxygenation with 100% oxygen and premedication with IV midazolam (0.02 mg/kg) and IV fentanyl (2 micrograms/kg) were administered before intubation.

For patients with palatal perforation, gauze pieces were used to cover the defect. Airway management was achieved using appropriately sized cuffed endotracheal tubes, confirmed via capnography. Perilaryngeal packing was performed with sterile roller gauze.

Postoperative Care:

Patients meeting extubation criteria were extubated on the operating table and transferred to the PACU or ward. Patients requiring tracheostomy underwent the procedure before or after surgery and were transferred to the PACU as needed. However, patients undergoing total maxillectomy or extensive surgical resection were tracheostomized before or after the surgical procedure and were shifted to PACU with oxygen as required. Hemodynamically unstable patients, patients with extensive surgery and those who showed no respiratory effort were transferred to the PACU with an endotracheal tube or tracheostomy tube in situ for further management.

Statistical Analysis:

Descriptive statistics were used for data analysis. Data were collected and compiled using Microsoft Excel. Statistical analysis was performed using SPSS version 23.0, with the Chi-square test employed where applicable. Results were reported in terms of frequency, percentage, means, and standard deviations (SD).

RESULTS

In the present study, a total of 110 patients were included, and follow-up was maintained for 30 days postoperatively. The study comprised 79 male patients (71.81%), with the majority falling within the age group of 51-60 years (31.81%) and 41-50 years (28.18%).

The most prevalent comorbidities observed in the study were diabetes mellitus (77.27%), followed by hypertension (39.09%) and ischemic heart disease (9.09%). Thirty-five patients were active smokers. Among diabetic patients, 54.65% had a duration of diabetes exceeding 10 years. The majority of patients were not vaccinated (88.18%), while 11.82% had received only one dose of the vaccine. (Table 1)

Mucormycosis was confirmed in 70.91% of cases through the KOH mount study. The CT severity score was >15 in 16.37% of patients. Clinically, the majority of patients presented with rhino-orbital involvement upon admission (74.55%). Most patients had previously received steroids (80%), anticoagulants (29.09%), and oxygen support or injection remdesivir (73.64%), as documented in their previous hospital admission records, discharge summaries, and patient histories. All patients were on Amphotericin-B at the time of surgery. Procedures performed included bilateral functional endoscopic sinus surgery (B/L FESS) (41.82%), B/L FESS + left maxillectomy (20%), B/L FESS + right maxillectomy (13.64%), and B/L FESS + total maxillectomy (20.0%). (Table 2)

Intubation was successful on the first attempt in 95 patients (86.36%), while others required the BURP manoeuvre (applying backwards, upward, rightward, and posterior pressure on the larynx) (21.82%), bougie (17.27%), or videolaryngoscopy (31.82%). Preoperative tracheostomy was performed in 11 patients. (Table 3)

The average duration of surgery was 142.23 $\pm$ 29.95 minutes, and the average duration of anaesthesia was 166 $\pm$ 50.59 minutes. Extubation on the operating table was

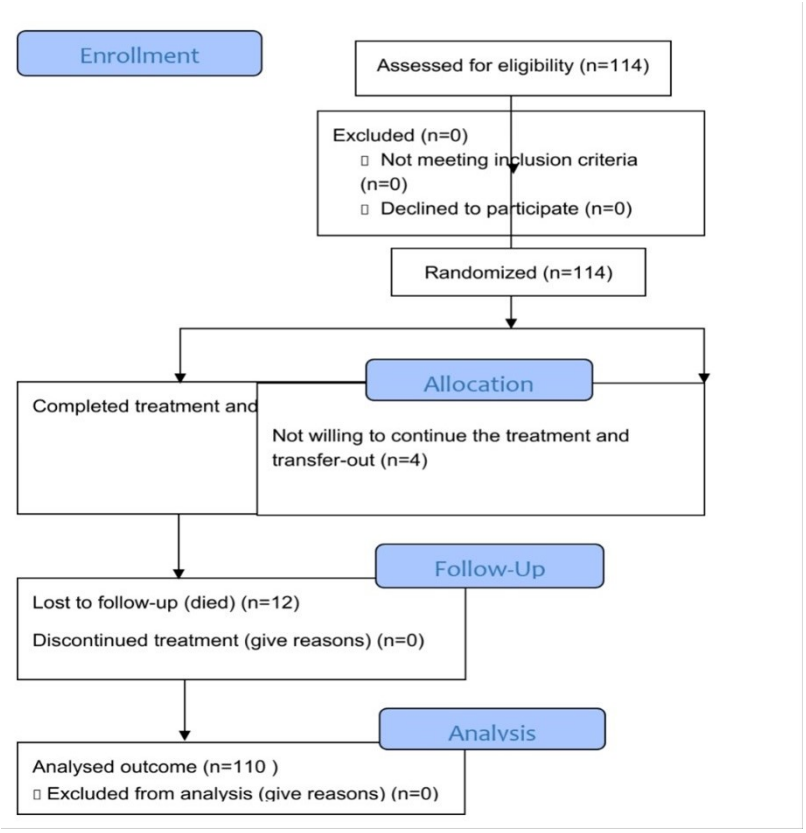

Figure 1: Flow Diagram of selection of patients

possible in 80% of cases, while the remaining required an average ICU stay of 9.83 ± 7.33 days. Inotropic support was necessary in 20% of patients. The majority underwent a single surgery (87.27%).

Most patients were successfully discharged (85.45%), while mortality was observed in 10.91% of cases. Frontal sinus abscess (6.36%) and maggots in the maxilla and sphenoid (0.91%) were noted during the 30-day follow-up. (Table 4)

DISCUSSION

Mucormycosis is a progressive, emerging, opportunistic fungal infection with a high risk of mortality. Being highly angioinvasive, mucormycosis may attack any organ system and may be accompanied by hemodynamic instability and difficult airway management.

The incidence rate of mucormycosis varies from 0.005 to 1.7 per million populations globally, whereas in the Indian population, its prevalence was 0.14 per 1000, which was about 80 times higher than in developed countries in the pre-COVID era. [4, 6] The incidence of mucormycosis has risen more rapidly during the second wave compared with the first wave of COVID-19 in India. However, changing host environment were causing their emergence as potential pathogenic organisms leading to high morbidity and mortality. [4]

A high suspicion for this disease must be considered in patients who are immunocompromised. Tissue necrosis, a hallmark of mucormycosis is often a late sign. [8] A recent review showed that the median time interval between diagnosis of COVID-19 and clinical diagnosis of mucormycosis infection was 15 days. [9] In this study, the average duration between COVID-19 and the first symptom of mucormycosis was 13.45+/- 6.89 days.

Awadhesh Kumar Singh et al. [1] studied 101 cases of mucormycosis in people with COVID-19 in which pre-existing diabetes mellitus (DM) was present in 80% of cases, corticosteroid intake for the treatment of COVID-19 was recorded in 76.3% of cases. They noted that the unholy trinity of diabetes, and rampant use of corticosteroids in a background of COVID-19 appears to increase mucormycosis. Given the large number of diabetic patients in India of almost 62 million, mucormycosis has caused a large public health burden. [10] Prakash H noted that diabetes mellitus was the underlying disease in 54–76% of mucormycosis cases. [6]

In this study, the majority (77.27%) of patients were found to be diabetic, among them 54.65% had duration of diabetes for more than 10 years and the rest were found to be recently diagnosed with DM. Glycemic control was of paramount importance in these patients for postoperative outcomes. We started perioperative intravenous insulin infusion in patients with deranged blood sugar levels to maintain it between 100-180 mg/dl with hourly monitoring.

Characteristics	No. of patients No. (%)
Age (in years)	
<40	18 (16.4)
41-50	31 (28.2)
51-60	35 (31.8)
61-70	20 (18.2)
≥ 71	6 (5.5)
Gender	
Male	79 (71.8)
Female	31 (28.2)
BMI (Mean±SD)	26±5.2
Comorbidity	
Diabetes mellitus	85 (72.3)
Hypertension	43 (39.1)
Smoking	35 (31.8)
Ischemic Heart Disease	10 (9.1)
Hypothyroidism	5 (5.6)
Bronchial asthma	3 (2.7)
Chronic Kidney Disease	1 (0.9)
Chronic myeloid leukemia	1 (0.9)
Vaccination	
Single Dose	13 (11.8)
No Dose	97 (88.2)

Table 1: General Characteristics of patients

Ritesh Gupta et al.[11] studied 115 patients with coronavirus-associated mucormycosis in which all patients had received corticosteroids. After surviving from COVID-19 pandemic, patients landed up into post-COVID-19 syndrome such as opportunistic fungal infection / bacterial infection or both

On logistic regression analysis, a CT scan-based score for severity of lung involvement was associated with mortality. In our study, 42.73% of patients had a CTSS (CT severity score) of more than 10, which was challenging in postoperative outcomes.

It is important for the anesthesiologist to know the severity of COVID-19 to anticipate the perioperative outcomes of the patients. In this study, among 80% of hospitalized patients for treatment of COVID-19 who received steroids and remdesivir as a COVID-19 management, 73.64% of patients required oxygen support, low molecular weight

Characteristics	No. of patients No. (%)
Mucormycosis	
Suspect	32 (29.1)
Proven	78 (70.1)
CT severity score	
NAD	27 (24.6)
<10	36 (32.7)
11-15	29 (26.4)
16-20	15 (13.6)
>20	3 (2.7)
Treatment received while covid-19 positive	
Steroids	88 (80.0)
Anticoagulants (LMWH/aspirin)	32 (29.1)
O2 support/ REMDESIVIR	81 (73.6)
Duration between Covid-19 and RO symptoms (in days)	13.45 ± 6.89
Clinical staging of ROC mucormycosis	
Sinusitis	7 (6.4)
Sino-orbital symptoms	82 (74.6)
Sino-orbital-cerebral symptoms	21 (19.1)
Duration between RO symptoms and surgery (in days)	21.33 ± 8.23
Day of Amp-B at the time of Surgery	
≤ 7	95 (86.4)
more than 7	15 (13.6)
B/L FESS	46 (41.8)
B/L FESS + partial maxillectomy	39 (35.5)
B/L FESS + total maxillectomy	22 (20.0)
B/L FESS + one eye enucleation	3 (2.7)

NAD: No abnormality detected.
Duration: between Covid-19 and RO symptoms and surgery (in days) is presented as Mean ± SD.
B/L FESS: bilateral functional endoscopic sinus surgery

Table 2: Pre-operative characteristics

Characteristics	No. of patients No. (%)
ASA status	
2	61 (55.5)
3	49 (44.5)
Mouth Opening (cm)	
1	7 (6.4)
2	32 (29.1)
3	58 (52.7)
4	13 (11.8)
Mallampati score	
1	18 (16.4)
2	38 (34.6)
3	42 (38.2)
4	12 (10.9)
Palatal eschar (+)	55 (50.0)
Intubation Attempts	
1	95 (86.4)
2	4 (3.6)
TRACHEOSTOMY	11 (10.0)
BURP manoeuvre	24 (21.8)
Bougie	19 (17.3)
Videolaryngoscopy	35 (31.8)

BURP manoeuvre: applying backward, upward, rightward and posterior pressure on the larynx.

Table 3: Anesthesia characteristics

Characteristics	No. of patients No. (%)
Average duration of surgery (min) Mean ± SD	142.2 ± 29.9
Average duration of anaesthesia (min) Mean ± SD	166 ± 50.6
Extubation	
On table	88 (80.0)
T PIECE (TRACHEOSTOMY)	9 (8.2)
Post OP ICU	63 (57.3)
Average ICU stay (days)	9.8 ± 7.3
Inotropic support	22 (20.0)
Mean days of hospitalization (SD)	14.6 (13.3)
Total surgeries	
1	96 (87.3)
2	14 (12.7)
Outcome	
Discharged	94 (85.5)
Died	12 (10.9)
Transfer out to other hospitals	4 (3.6)
30 days outcome	
Frontal Sinus Abscess	7 (6.4)
Maggots in the maxilla and sphenoid	1 (0.9)

Table 4: Post-operative characteristics

heparin was given to 29.09% of patients which suggested the severity of disease. CTSS was more than 15 in 16.37% of patients.

Considering the emergency nature of the disease, peri-operative anaesthesia management was highly important due to the risk of comorbidities and rapid progression of the disease. Preoperatively for optimisation of chest, blood sugar level, hemodynamic status and sepsis control, we started patients on nebulisation, regular insulin according to blood sugar levels, adequate fluid resuscitation and antifungal agents along with proper antibiotics respectively.

Sen M et al. [12] studied 2826 patients of rhino-orbital-cerebral mucormycosis (ROCM). The mean age of patients was 51.9 years with a male preponderance (71%). Choksi T et al. [13] studied 73 consecutive patients with CAM with a mean age of 53.5 ± 12.5 years, 48 (66%) were men.

In our study, the mean age of patients was 52.4 +/- 11.7 years (21-78 years) and 72.82% were men. 16.36% of patients were in the age group of <40 years, 28.18% of patients were in the age group of 41-50 years, 31.82% were in the age group of 51-60 years, 18.18% were in 61-70 years and 5.45 % in the age group of ≥ 71 years.

Due to long-standing DM, facial disfigurement, oedema of tissue associated with fungal debris, bone disruption, palatal perforation, fragility of involved tissue, loose/ missing teeth can cause reduced mouth opening, limitation of space for a laryngoscopy, worsening of MPC grading (Mallampati classification), painful mouth opening, decreased neck movements which can lead to difficulty in mask ventilation and endotracheal intubation. Palatal invasion/ erosion leading to fistula track, draining fungal debris into the oral cavity, can cause aspiration and difficult intubation. Karaaslan E. [14] study, out of 3 patients with diffuse fungal debris in the oropharyngeal region, in one patient endotracheal intubation could not be performed with direct

laryngoscopy due to supraglottic oedema and thus was performed with video laryngoscopy.

In this present study, we encountered mouth openings of 1 and 2 cm in 39 patients (35.48%). MPC scores were 3 and 4 in 42 and 12 patients respectively. Palatal eschar was present in almost 50% of our patients. Considering the above scenario, we kept all our difficult intubation equipment cart containing appropriate-sized nasopharyngeal airways, oropharyngeal airways, smaller-sized cuffed endotracheal tubes, stylet, gum-elastic bougies, laryngeal mask airways, video laryngoscope, fibre-optic bronchoscope, emergency tracheotomy ready to avoid difficult airway management and we consider all our patient as an anticipated difficult endotracheal intubation. Thus, intubation was performed with videolaryngoscopy in 32 patients while bougie was required with direct laryngoscopy in 19 patients and 24 patients were managed with BURP (applying backward, upward, rightward and posterior pressure on the larynx) manoeuvre. Rest patients underwent elective tracheostomy due to the extensive nature of the disease, compromised airway and need for postoperative airway management.

Amphotericin-B acts by binding to the sterol component, ergosterol, of the cell membrane of susceptible fungi forming transmembrane channels leading to alterations in cell permeability through which monovalent ions (Na+, K+, H+, and Cl−) leak out of the cell resulting in cell death. [15] Its systemic treatment can lead to nephrotoxicity, hypotension, arrhythmias and allergic manifestation which can alter the anaesthesia outcome in these patients.

All our patients received Amphotericin-B. Keeping this in mind our major concern was to avoid further development of acute renal failure in our patients by maintaining adequate mean arterial pressure (MAP) and cardiac output. Judicious fluid administration was done. 42.72% of patients received blood and blood products while the rest managed with crystalloids. If target MAP was not achieved on fluid administration or blood loss replacement with blood and blood products, vasopressors were initiated like noradrenaline, adrenalin, and dopamine on a timely basis to prevent multi-organ dysfunction which can further deteriorate the prognosis of patients. Inotropic support was initiated in 20% of our patients perioperative.

The average duration of surgery was 142.23 ± 29.95 minutes and the average duration of anaesthesia noted was 166 +/- 50.59 min. We successfully could extubate 80% of our patients on the operative table and 8.18% of patients were shifted to SICU (surgical intensive care unit) with tracheostomy tube with T piece while 11.82 % of patients were shifted on ventilator to COVID dedicated SICU because of extensive nature of debridement, hemodynamic instability, delayed recovery and further management. Patients who underwent total maxillectomy were preferred for elective ventilation in the SICU with closed monitoring.

Jeong et al. [16] found that early diagnostic procedures (within 16 days of symptom onset) were associated with improved long-term survival of patients with invasive mucormycosis infection. In this study, the average duration between rhino-orbital symptoms and surgery was 21.33 ± 8.23 days. This may be due to patients not being aware of the nature of the disease and negligence towards red flag signs by patients. 19.09% of patients came directly with orbital involvement; this may be due to the rapid progression of the disease.

In this study, the average mortality was 10.91% and the average duration of ICU stay was 9.83+/-7.33. Patients' follow-up was taken for 30 days postoperatively, 85.45% of patients were discharged from the hospital, among which 6.36% patients came with frontal sinus abscess while one patient came with maggots in maxilla and sphenoid which was treated subsequently.

Corticosteroids and DM are the most important predisposing factors in the development of COVID-19-associated ROCM. COVID-19 patients must be followed up beyond recovery. We believe these results will help develop strategies for managing patients with ROC mucormycosis for surgical debridement.

CONCLUSION

COVID-19-associated mucormycosis had high morbidity and mortality due to delayed diagnosis and rapid progression of disease. Perioperative anaesthesia care plays an important role towards the management and outcome of ROC mucormycosis. Difficult intubation and mask ventilation are anticipated due to fungal debris and supraglottic oedema in the oropharynx of the patient.

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