Original Article

Perioperative anesthesia challenges and outcomes of patients with Rhino-Orbito-Cerebral Mucormycosis during the second wave of COVID-19 pandemic: An observational study

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Abstract

Background and Aims: A rapid surge in rhino-orbito-cerebral mucormycosis (ROCM) cases was reported during the second wave of COVID, especially in India, needing extensive surgical debridement along with medical management. The present study was planned to observe perioperative anesthesia challenges and outcomes of patients with ROCM during the second wave of the COVID-19 pandemic. The primary objective was to observe intraoperative anesthesia challenges and the secondary objectives were to observe postoperative challenges and outcomes of patients.

Material and Methods: This was a single-centered, bidirectional (retrospective and prospective) observational study, conducted at a tertiary care center. We enrolled 218 adult patients scheduled for surgical debridement of ROCM under general anesthesia. Demographics, COVID status, comorbid illness, intraoperative challenges (difficult airway, hemodynamic instability, blood loss), and postoperative outcome (postoperative mechanical ventilation, and mortality rate) were noted.

Results: The majority of the patients were males (71%) and had diabetes mellitus (54%). COVID-associated mucormycosis was seen in 67% and 41% of them received steroids. Post-induction hypotension was noted in 20.6% of patients, and 14.2% had intraoperative hypotension out of which 5.5% required vasopressor support. Difficult mask ventilation and difficult intubation were reported in 7.3% and 6.4% of patients, respectively. No significant difference was found among intraoperative challenges when COVID mucormycosis was compared to non-COVID mucormycosis. Postoperative mechanical ventilation and ICU care were required in 41.3%, whereas mortality was seen in 11.5% of patients. The mortality was significantly more ($P = 0.041$) in patients with COVID mucormycosis (13%) compared to that with non-COVID mucormycosis (4.2%).

Conclusion: Diabetic male patients who received steroids during COVID illness are at the highest risk of developing ROCM. Difficult airway and hemodynamic instability, are significant perioperative challenges encountered by anesthesiologists. Postoperative ICU management is crucial for decreasing postoperative morbidity and mortality.

Keywords: Anesthesia, COVID-19, diabetes mellitus, mucormycosis, outcome

Introduction

During the second wave of COVID-19, increased cases of COVID-associated rhino-orbito-cerebral mucormycosis (ROCM) have been reported worldwide, especially in India.[1,2] Mucormycosis is a rapidly progressive, opportunistic fungal infection with a propensity to involve multiple organs and is associated with high mortality.[3] The most common causes attributed to the rise of COVID-associated

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mucormycosis are diabetes, especially uncontrolled and diabetic ketoacidosis, long-term use of corticosteroids, and prolonged stay in the intensive care unit.[2,4,5] ROCM usually originates from the paranasal sinuses, causing bone destruction and subsequent invasion of the orbit, eyes, and brain. Successful management of mucormycosis involves a multidisciplinary team and mainly depends on early diagnosis and management by early and complete surgical debridement of infected tissue, in addition to rapid administration of systemic antifungal therapy.[5,6] Perioperative anesthesia management in patients undergoing ROCM surgery can be challenging, because of likely airway involvement, uncontrolled blood sugar levels, problems associated with long-term use of corticosteroids, and amphotericin.[7,8] Airway management of these patients is very important and can be challenging because the fungal debris in the oropharyngeal region and supraglottic edema can lead to difficult mask ventilation and difficult intubation. To the best of our knowledge, there are very few studies describing the anesthetic management of patients with mucormycosis and that too have observed a limited number of patients. We conducted a bidirectional observational study intending to observe the perioperative anesthesia challenges and outcomes of patients undergoing surgical resection for ROCM under general anesthesia. Our primary objective was to observe the intraoperative anesthesia challenges, and our secondary objectives were to observe the postoperative challenges and outcomes of these patients till discharge.

Material and Methods

Ethics approval was provided by the AIIMS, Jodhpur, Institutional Ethics committee (AIIMS Jodhpur, IEC, India) with the certificate reference number: AIIMS/IEC/2021/3555 on 17/06/21. This bidirectional (retrospective and prospective) observational study was carried out at the Department of Anesthesiology and Critical Care, AIIMS, Jodhpur. All patients who have undergone surgery (endoscopic or open) for ROCM under general anesthesia from April 2021 to July 2021 were included.

For retrospective analysis, the data were retrieved from patient files, pre-anesthetic and operative records, and also from the computerized hospital information system. Any missing or uncertain data were collected telephonically from the patients or family members. For prospective analysis, data of all patients undergoing surgery for ROCM under general anesthesia were recorded and analyzed.

Demographic details, current COVID status, severity and management of current or past COVID infection, treatment received for COVID and mucormycosis, and associated comorbid illness were noted for all enrolled patients. The intraoperative anesthesia challenges such as difficult mask ventilation (not possible to provide adequate ventilation confirmed by end-tidal carbon dioxide detection, because of one or more of the problems such as inadequate mask seal, excessive gas leak, or excessive resistance to the ingress or egress of gas), difficult intubation (Cormack–Lehane grade III or IV), post-induction or intraoperative hypotension (defined as mean arterial pressure <60 mmHg) and requirement of vasopressor (norepinephrine), blood loss and transfusion requirement, and complications were noted. Postoperative outcomes of these patients till discharge in terms of the requirement of mechanical ventilation or intensive care unit and mortality rate were recorded.

The data collected were compiled and analyzed using SPSS22. Categorical variables are expressed as the number and percentage, whereas continuous variables are summarized as the mean and standard deviation for normally distributed data, and the median and interquartile range (IQR) for skewed or non-normally distributed data. The normality of distribution for continuous variables was confirmed with the Kolmogorov–Smirnov test. Demographic details, clinical findings, perioperative anesthesia management and challenges, and postoperative outcomes were plotted on an MS Excel spreadsheet. Results are presented in numbers/mean and expressed in terms of percentage.

Results

A total of 218 patients underwent surgery (endoscopic or open) for ROCM under general anesthesia from April 2021 to July 2021. Retrospective data were collected and analyzed for 120 patients, whereas 98 patients were enrolled prospectively. The demographic profile and patient characteristics of all patients are depicted in Table 1. The mean age of patients was 46.98 ± 12.33 years and the mean weight was 68.84 ± 11.03 kg. Out of 218 patients, 155 patients (71%) were males and the majority (60.1%) of them belonged to the ASA II category.

COVID-associated mucormycosis was found in 67% of the patients, out of which 42.7% had post-COVID mucormycosis, whereas 24.3% of the patients were COVID

Table 1: Demographic distribution

Demographics	Patients
Male/female	155/63
ASA I/II/III	35/131/52
Age (mean±SD)	46.98±12.33
Weight (mean±SD)	68.84±11.03
Sinonasal/orbital/cerebral extension	198/13/7

positive with concomitant mucormycosis. Thirty-three percent of the patients had mucormycosis without a present or past history of COVID. Of all the patients having a present or past COVID (146), 77.4% had mild disease requiring home isolation, 19.9% had moderate disease requiring hospital admission for oxygen therapy, and only 2.7% had a severe form of the disease requiring ICU admission. Of all COVID patients, 41% received steroids in the form of dexamethasone or methylprednisolone, out of which 70% received steroids for more than 7 days. Most patients (90%) received dexamethasone in a dose of 6 or 8 mg and for a mean duration of 7.8 days. The exact data about the dose and duration of steroid therapy and other drugs received for COVID illness could not be retrieved as most of the patients had received steroids and other drugs at multiple centers, during active COVID and the records were not available. Moreover, because of the involvement of different clinicians at different centers, steroid use was not standardized. The most common comorbid illness seen was diabetes mellitus (54.1%), followed by hypertension (11.5%), and coronary artery disease (4.6%). Of all diabetic patients, 52.54% of patients were on insulin, 47.46% of patients were on oral hypoglycemic agents, and 59.3% of them had uncontrolled blood sugars. Among 218 patients, 202 (92.66%) had rhinomaxillary mucormycosis, 6.4% of patients had rhino-orbital mucormycosis, and only 2 patients (0.92%) had cerebral extension [Figure 1].

Intraoperative anesthesia concerns and challenges are illustrated in Figure 2. Preoperatively, all patients were hemodynamically stable and were induced with a titrated dose of propofol, and all patients were maintained on isoflurane with Minimum alveolar concentration (MAC) 1.0–1.2. Post-induction hypotension was noted in 20.6% of patients and 14.2% had intraoperative hypotension, out of which 5.5% required vasopressor (norepinephrine) support. In 7.3% of patients, difficult mask ventilation was noted and difficult intubation was seen in 6.4%. Intraoperative hypokalemia ($K^+ < 3.5$) was noted in 6.4% of patients, for which potassium replacement was required. Blood loss more than maximum allowable blood loss (MABL) requiring intraoperative blood transfusion was noted in 12.4% of patients. Intraoperative anesthesia concerns and challenges were compared between COVID and non-COVID mucormycosis, and no significant difference was found among any of the anesthesia challenges [Table 2].

Postoperative anesthesia challenges are illustrated in Figure 3. Among all operated patients, 59.6% were extubated at the end of the surgery. Out of them, only one patient needed reintubation because of inadequate respiratory efforts and tachypnea after extubation. Also, 41.3% of patients required postoperative mechanical ventilation and ICU care for a mean duration of 4.4 days. All patients were followed until discharge and postoperative mortality was seen in 11.5% of patients. Refractory hypoxia was found to be the main cause of mortality, seen in 64% of the patients, whereas in the remaining patients, refractory sepsis was seen as a cause of death. The mortality was significantly higher in patients with COVID mucormycosis (13%) as compared to non-COVID mucormycosis (4.2%) with $P < 0.05$.

Patients requiring postoperative mechanical ventilation and patients who had postoperative mortality were analyzed to identify the risk factors associated with the requirement of postoperative mechanical ventilation and mortality in patients undergoing surgical resection for ROCM under general anesthesia. No significant association was found between any of the factors (e.g., hypotension, diabetes, blood loss, COVID

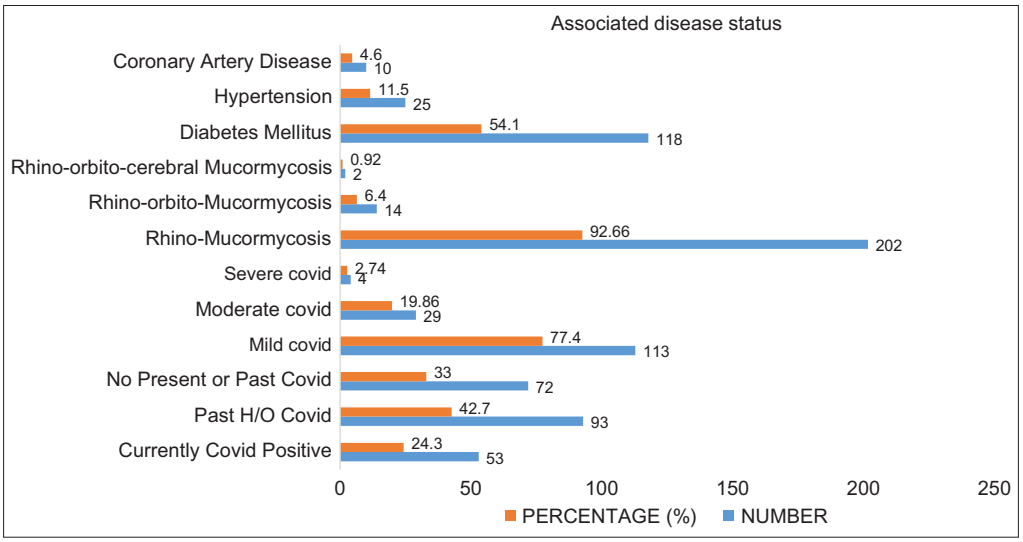

Figure 1: The distribution of various diseases and co-morbid conditions

Table 2: Comparison of perioperative challenges in COVID and Non-COVID mucormycosis

Parameters (in %)	COVIDmucor (100%)	Non-COVID mucor (100%)	*P*	Odds ratio (CI)
Difficult BMV	8.2	5.6	0.478	1.5 (0.473–4.9)
Difficult Intubation	6.2	6.9	0.835	0.88 (0.284–2.75)
Blood loss	13.8	9.9	0.412	1.46 (0.588–3.64)
Hypotension (postinduction)	18.5	25	0.264	0.681 (0.346–1.34)
Hypotension (intraop)	15.2	12.7	0.623	1.23 (0.535–2.83)
Postop ventilation/ICU	39.7	44.4	0.506	0.824 (0.465–1.458)
Mortality	13	4.2	0.041	3.44 (0.983–12.03)

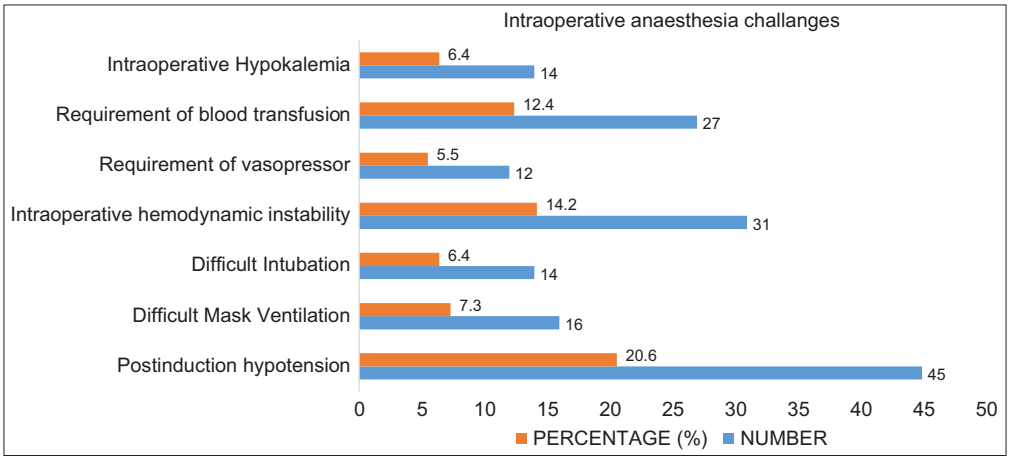

Figure 2: The distribution of various challenges during the intraoperative period

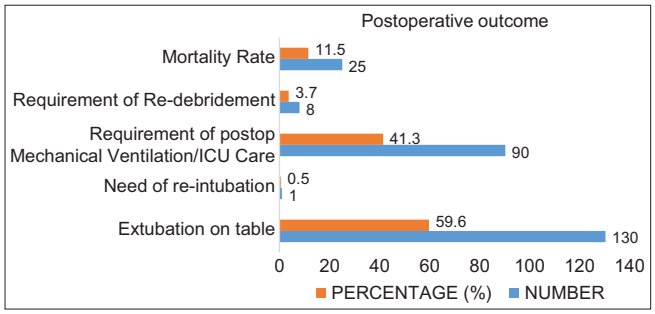

Figure 3: The distribution of various postoperative outcomes

status, and hypokalemia) and the requirement of post-operative ventilation/ICU admission. A significantly ($P < 0.05$) higher mortality was observed in patients who were currently COVID positive, had severe COVID infection, and patients who had intraoperative hypotension and required postoperative mechanical ventilation.

Discussion

In this bidirectional observational study, 218 patients of ROCM during the second wave of the COVID-19 pandemic were observed for perioperative anesthesia challenges. Difficult airway, hemodynamic instability, and requirement of postoperative mechanical ventilation were the main anesthesia challenges encountered, which were more in COVID mucormycosis patients compared to non-COVID mucormycosis though the difference was not statistically significant.

In the present study, the majority of patients were males (71.1%), similar to the study by Singh *et al.*[9] and a systematic review was undertaken by Pal *et al.*[10] where they found around 78% of the patients with mucormycosis to be males. This is found as per the association of COVID-19 infectivity with the male gender as compared with females in India.[11]

Uncontrolled diabetes, long-term use of corticosteroids, and COVID infection resulting in prolonged ICU stay are the most common causes attributed to the rise of COVID-associated mucormycosis.[2,4] DM is the most common predisposing factor and is seen in 50–70% of patients diagnosed with mucormycosis.[4,12,13] Hyperglycemia is known to cause phagocyte dysfunction, impaired intracellular killing, and chemotaxis, increasing the risk of mucormycosis.[14] In our study, we observed similar results with 54% of patients with mucormycosis suffering from DM and most patients (59.3%) had uncontrolled blood sugar levels. Our results were similar to a recent multicentric study conducted by Prakash *et al.*[15] on mucormycosis in India, in which 57% of patients were found to have uncontrolled diabetes mellitus.

For COVID-19 treatment, the landmark RECOVERY trial[16] and other trials[17] proved corticosteroids to be the only effective

treatment and that is the reason corticosteroids were used in high doses during the second wave of COVID-19, which itself was a risk factor for COVID-associated mucormycosis. Corticosteroids are known to exaggerate blood glucose levels and cause immunosuppression and lymphopenia predisposing to mucormycosis.[18,19] However, the ongoing research and changing evidence of type, dose, and duration of steroid use during pandemic allowed the clinicians to use steroids in different doses and for different durations in a non-standardized way.[20]

In our study, 41% of all COVID patients received steroids in the form of dexamethasone or methylprednisolone and 70% of them received steroids for more than 7 days. Mucormycosis in patients infected with COVID-19 is common because of hyperglycemia and alteration of iron metabolism seen with COVID-19 infection.[18,21]

The data revealed that 67% of patients had COVID-associated mucormycosis, 42.7% of whom had a history of COVID infection, and 24.3% were currently COVID positive with concomitant mucormycosis. Similar to our results, Pal *et al.*[10] reported that 37% of the patients with mucormycosis had a history of COVID infection. Moorthy *et al.*[19] reported that increased incidence of ROCM is not only caused by diabetes, steroid administration, and COVID-19 infection independently but this trinity was commonly seen during the COVID-19 pandemic, which potentiated immune dysregulation resulting in fungal invasion and tissue necrosis.

Mucormycosis patients, especially those with ROCM have anticipated a difficult airway. Both mask ventilation and endotracheal intubation can be difficult because of distorted facial anatomy, epiglottitis, and supraglottic edema.[7,22] Moreover, most patients were diabetic, in whom the involvement of the atlantooccipital joint as a part of the diabetic stiff joint syndrome, makes laryngoscopy difficult. Erden *et al.*[23] reported a statistically significant increase in difficult laryngoscopy (18.75% vs. 2.5%) in type 2 diabetics versus non-diabetics. The incidence of difficult mask ventilation and difficult intubation reported in our study was 7.3% and 6.4%, which is higher than that reported in the general population (5% and 5.8%, respectively).[24] In addition to anticipated difficulty, airway handling of patients with present or past COVID is strenuous due to the risk of self-infection.[25] In our study, all mucormycosis patients with active COVID-19 infection were operated on in COVID-designated operating theaters, with all due precautions such as rapid sequence induction and the use of a video-laryngoscope for securing the airway.

In addition to the difficult airway, another important intraoperative challenge was hemodynamic instability. In addition to common causes of hypotension such as vasodilation due to anesthetic drugs, systemic inflammation, and intravascular hypovolemia due to bleeding, another important cause specific to mucormycosis patients is the prolonged use of steroids.[26] Patients on prolonged steroid therapy may affect the hypothalamic–pituitary–adrenal (HPA) axis causing its suppression, which leads to decreased cortisol production, known as secondary adrenal insufficiency. Inadequate cortisol production may predispose to vasodilatation and hypotension, which could be one of the reasons for perioperative hypotension and the requirement for vasopressors.[27] Another important concern and reason for intraoperative hypotension in patients being operated on for ROCM is the risk of excessive blood loss due to the use of anticoagulants or antiplatelets in patients infected with COVID.[28]

Amphotericin B, used as the first-line drug for medical management of mucormycosis increases the risk of nephrotoxicity, and electrolyte imbalance such as hypokalemia, hypomagnesemia, and hypotension.[7,8] Although providing anesthesia to mucormycosis patients receiving amphotericin B special alertness is required for renal, electrolytes, and hemodynamic complications. Anesthetists should pay particular attention to achieving preoperative hemodynamic stability and maintaining adequate mean arterial pressure and cardiac output to maintain adequate renal perfusion to avoid further renal insult.[7,8] COVID-19 infection adversely affects respiratory function and can increase the risk of perioperative pulmonary complications.[29,30] However, no adverse pulmonary complications were reported in our study, this may be because only 2.7% of our patients had severe COVID-19 infection.

Mucormycosis is associated with mortality of 50% or higher even after prompt diagnosis and treatment.[31] The literature indicates that the use of surgical treatment in addition to medical management has decreased the mortality rate in patients of ROCM from 88% to 21%.[32,33] Spellberg *et al.*[33] reported that in mucormycosis patients receiving antifungal treatment alone, a 70% mortality rate was seen compared to only 14% in patients who received both antifungal and surgical treatment. In our study, the observed mortality rate was only 11.5%. The improved survival in our patients was likely because of more aggressive combined medical and surgical management, which is known to decrease the mortality rate in patients with ROCM.[32,33] In our study, severe COVID infection, intraoperative hemodynamic instability, and the requirement for postoperative mechanical ventilation were the observed risk factors for mortality in patients undergoing surgical resection for ROCM. Postoperative ICU management is very important in this group of patients due to associated comorbidities,

compromised lungs, and risk of rapidly progressive infection even after surgery.

Our study has several limitations. First, the study is bidirectional (retrospective and prospective). Data of approximately 55% of patients were analyzed retrospectively from anesthesia and hospital records. Second, our study is a single-center study. Although we have analyzed data of a significant number (218) of patients, all of them were from a single center. The mucormycosis incidence with COVID-19 and perioperative challenges faced by other anesthesiologists globally could not be addressed in this study. Another limitation is that we could not collect data regarding long-term outcomes, as the postoperative outcome was recorded only until the discharge of the patient.

In conclusion, most patients were males, with a history of diabetes mellitus, and had received steroids during COVID-19 management. Difficult airway, hemodynamic instability, glycemic control, blood loss, and consequences of amphotericin B can be important perioperative challenges, for which all anesthesiologists should be ready and ensure appropriate care and safety. Postoperative ICU care and management are very important and play a crucial role in decreasing postoperative morbidity and mortality in patients with mucormycosis.[34]

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Conflicts of interest

There are no conflicts of interest.

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