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Anesthetic Management of Mucormycosis Cases Requiring Surgical Debridement

Cerrahi Debridman Gerektiren Mukormikozis Vakalarına Anestezik Yaklaşım

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ABSTRACT

Objective: Mucormycosis is a rare, progressive, and life-threatening fungal infection that occurs in immunocompromised patients. In the present study, we aimed to evaluate the perioperative challenges in the anesthetic management of mucormycosis patients.

Methods: Patients over 18 years of age who underwent surgery for mucormycosis within a 3-year period between January 1, 2020 and December 31, 2022 were included in the study. Perioperative records were retrospectively evaluated.

Results: During this period, 25 of 47 cases of mucormycosis were surgically treated. Data from these 25 cases were analyzed. Twelve (48%) patients had a diagnosis of rhinocerebral, 7 (28%) rhino-orbital, 5 (20%) rhino-orbito-cerebral and 1 (4%) rhino-pulmonary mucormycosis. All patients had comorbidities. The most common comorbidities were diabetes mellitus in 20 (80%), followed by hypertension in 12 (48%), acute kidney injury in 7 (28%) and coronary artery disease in 5 (20%) patients. Six (24%) patients had a history of COVID-19 infection and were treated with steroids. Intubation was difficult in 2 (8%) patients. Two (8%) patients had intraoperative hemodynamic instability requiring inotropes. There were 17 (68%) patients, 6 (24%) of whom were intubated, who were transferred to the intensive care unit (ICU). The median length of stay in the ICU was 22.7 days and the total length of stay was 42 days. Eleven (44%) patients required mechanical ventilation. Mortality occurred in 12 (48%) patients.

Conclusion: Anesthetic management of surgical debridement for mucormycosis is challenging. Challenges include difficult intubation and renal dysfunction. Postoperative follow-up in the ICU is important due to rapid progression and comorbidities.

Keywords: Mucormycosis, COVID-19, anesthesia

ÖZ

Amaç: Mukormikoz nadir görülen, hızlı ilerleyen ve sıklıkla ölümle sonuçlanan, bağışıklık sistemi baskılanan olgularda görülen bir mantar enfeksiyonudur. Bu çalışmada, mukormikoz hastalarının anestezi yönetiminde karşılaşılan perioperatif zorlukları değerlendirmeyi amaçladık.

Yöntem: Çalışmaya 01.01.2020 ve 31.12.2022 tarihleri arasında 3 yıllık dönemde mukormikoz nedeniyle ameliyat edilen 18 yaş üstü vakalar dahil edildi. Perioperatif kayıtlar retrospektif olarak incelenerek değerlendirildi.

Bulgular: Bu sürede 47 mukormikozis vakasının 25'i operasyona alınmıştır. Bu vakaların verileri çalışma için analiz edildi. Oniki (%48) hasta rinoserebral, 7 (%28) hasta rino-orbital, 5 (%20) hasta rino-orbito-serebral, 1 (%4) hasta rino-pulmoner mukormikoz tanısı almıştır. Tüm vakalarda eşlik eden komorbidite mevcuttu. En sık görülen komorbidite 20 vakada (%80) diabetes mellitus iken, bunu 12 vakada (%48) hipertansiyon, 7 vakada (%28) akut böbrek hasarı ve 5 vakada (%20) koroner arter hastalığı izlemiştir. Altı vakada (%24) COVID-19 enfeksiyonu öyküsü mevcuttu ve steroid tedavisi almışlardı. Entübasyon 2 vakada (%8) zordu. İki vakada (%8) intraoperatif hemodinamik instabilite ve inotrop gereksinimi vardı. Vakaların 6'sı (%24) entübe olmak üzere 17 (%68) vaka Yoğun Bakım Ünitesi'ne (YBÜ) çıkarıldı. Yoğun Bakım Ünitesinde ortalama yatış süresi 22,7 gün, toplam hastane yatış süresi ise 42 gündü. Onbir (%44) vaka mekanik ventilatöre ihtiyaç duydu. Mortalite 12 hastada (%48) görüldü.

Sonuç: Mukormikozda cerrahi debridmanın anestezi yönetimi zordur. Zorluklar arasında zor entübasyon ve böbrek fonksiyon bozukluğu yer alır. Bu vakaların cerrahi sonrası hızlı progresyon ve komorbiditeler nedeniyle YBÜ'nde takibi önemlidir.

Anahtar sözcükler: Mukormikozis, COVID-19, anestezi

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INTRODUCTION

Mucormycosis is a rare, acute, aggressive, rapidly progressive, and life-threatening angio-invasive fungal infection that occurs in immunocompromised patients (1). Risk factors associated with mucormycosis include uncontrolled diabetes mellitus, hematopoietic stem cell and solid organ transplantation, corticosteroid therapy, neutropenia, or drug-induced immunosuppression (2-4). During the pandemic, there has been an increase in cases associated with COVID-19 infection. The frequent use of corticosteroids in these patients may have contributed to COVID-associated mucormycosis (5).

Rhino-orbital, rhino-sinusal, and rhino-orbito-cerebral mucormycosis are the most commonly affected sites. Despite early aggressive combined surgical and medical therapy, the prognosis of mucormycosis is poor. The characteristic sign of mucormycosis is tissue necrosis, which is often a late sign. The mortality rate of mucormycosis is 46% worldwide (6).

For anesthesiologists, surgical debridement of mucormycosis is noteworthy because of the difficulty of the procedure itself, as well as the immunosuppression and comorbidities present in these patients. In the present retrospective study, we aimed to evaluate the demographics, procedural data, in-hospital mortality, and perioperative challenges in the anesthetic management of mucormycosis patients undergoing surgery under general anesthesia during the pandemic.

MATERIAL and METHODS

After obtaining ethics committee approval (E2-23-3474), all medical and operating room records of patients over 18 years of age who underwent surgery for mucormycosis within a 3-year period between 01.01.2020 and 12.31.2022 were retrospectively reviewed and evaluated. A total of 47 patients presented with mucormycosis during this 3-year period, of which 25 patients underwent surgical debridement under general anesthesia. Data from these 25 cases were analyzed for the study.

In this single-center, hospital-based retrospective study, demographic parameters including age, sex, American Society of Anesthesiologists physical status (ASA), patient comorbidities, covid disease, sites of mucormycosis, treatment received, laboratory parameters including complete blood count, liver and kidney function tests, coagulation profiles, blood glucose, HbA1c and serum electrolytes, intra-operative hemodynamic instability and inotrope requirements, duration of surgery and anesthesia, patients transferred from the operating room with an endotracheal tube or tracheostomy, patients requiring postoperative intensive care unit (ICU) stay, patients requiring mechanical ventilation, length of hospital stay, and mortality were evaluated.

Statistical Analysis

The study design was descriptive in nature and followed a retrospective record review design. We included the records of all patients (n=25) who were admitted to our center and underwent surgery for mucormycosis. Data related to the variables selected in the study were extracted from the records and entered into MS Excel software (Microsoft Inc.) for summative analysis. The data obtained in the study were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 22.0 (IBM SPSS 22.0 for Windows, Armonk, New York, United States). Shapiro- Wilk Test was used for evaluating normal distribution. Continuous data with normal distribution were expressed as mean ± standard deviation. Data not normally distributed were expressed as median. Categorical data were expressed as number (n) and percentage (%).

RESULTS

During the 3-year period between 01.01.2020 and 31.12.2022, 47 patients were diagnosed with mucormycosis. Twenty-five of the 47 cases underwent surgery and data from these 25 cases were analyzed for the study. The demographic and clinical characteristics of these cases are shown in Table I. In the study, we found that the mean age of the patients was 52.57 ± 18.77 years and 68% of the patients were male and 32% of the patients were female. Thus, surgical debridement of mucormycosis was performed significantly more often in males than in females.

Twelve (48%) patients had a diagnosis of rhinocerebral, 7 (28%) rhino-orbital, 5 (20%) rhino-orbital-cerebral and 1 (4%) rhino-pulmonary mucormycosis. All patients had comorbidities. The most common comorbidities were diabetes mellitus in 20 (80%), followed by hypertension in 12 (48%) and renal disease in 7 (28%). Six (24%) patients were reported to be using immunosuppressants. The incidence of coronary artery disease, cerebrovascular disease, and malignancy was 5 (20%), 4 (16%), and 4 (16%) patients, respectively. Six (24%) patients had COVID-19 infection and were treated with steroids. The most common symptoms were ocular pain and ocular swelling in 15 (60%) and 12 (48%) patients, respectively.

Table II shows the antifungal treatment of the patients. Among the antifungal drugs, Amphotericin-B was the most commonly used drug. Twenty patients (80%) received Amphotericin-B alone or in combination with Posaconazole.

The incidence of perioperative events is shown in Table III. Two (8%) patients with rhinocerebral and facial cutaneous mucormycosis experienced difficult intubation, which was resolved using videolaryngoscopy and gum elastic bougie. In one patient, tracheostomy was performed under sedo-

Table I: Demographic and Clinical Characteristics of Study Cases (n=25)

Variables	Frequency (%) Mean ± SD
Age (years)	52.57 ± 18.77
Weight (kg)	75.83 ± 16.96
Sex	
Male	17 (68)
Female	8 (32)
ASA	
II	1 (4)
III	17 (68)
IV	7 (28)
Diagnosis	
Rhino-cerebral	12 (48)
Rhino-orbital	7 (28)
Rhino-orbito-cerebral	5 (20)
Rhinopulmonary	1 (4)
Comorbidities	
Diabetes mellitus	20 (80)
Hypertension	12 (48)
Renal Disease	7 (28)
Immunesuppression	6 (24)
Coronary Artery Disease	5 (20)
Cerebrovascular Disease	4 (16)
Malignancies	4 (16)
COVID	6 (24)
Symptoms	
Eye pain	15 (60)
Eye swelling	12 (48)
Diminished vision	7 (28)
Ptosis	6 (24)
Swelling on face	5 (20)
Facial Pain	3 (12)
Headache	2 (8)
Facial Paralysis	2 (8)
Nasal discharge	1 (4)

ASA: American Society of Anesthesiologists.

Table II: Antifungal Treatment of the Cases (n=25)

Variables	n/ Frequency (%)
Amphotericin B	13/52
Amphotericin B and Posaconazole	7/28
Posaconazole	2/8
Fluconazole	1/4
Voriconazole	1/4

Table III: Incidence of Perioperative Events and Mortality (n=25)

Variables	Frequency (%) / Mean ± SD
Difficult intubation	2 (8)
Tracheostomy	1 (4)
Intraoperative hemodynamic instability	2 (8)
Intraoperative inotrope requirement	2 (8)
Shifted to patient services	8 (32)
Shifted to ICU	17 (68)
Extubated	19 (76)
Shifted to ICU intubated	6 (24)
Postoperative MV requirement	11 (44)
Mean number of days on MV	7.72 ± 15.01
Mean number of days in ICU	22.7 ± 19.79
Mean total number of days in hospital	42 ± 25.93
Mortality	12 (48)
Mean mortality time in days	31.6 ± 20.91

ICU: Intensive Care Unit, **MV:** Mechanical Ventilator.

analgesia due to a submandibular mass. Two (8%) patients had intraoperative hemodynamic instability and required inotropes. Seventeen patients (68%) were transferred to the ICU for further management and continuous hemodynamic monitoring. Of those, six (24%) required intubation upon admission to the ICU. Eleven (44%) patients required mechanical ventilation, with an average duration of 7.72 days. The mean length of ICU stay was 22.7 days, and the total length of hospitalization was 42 days. Mortality occurred in 12 patients (48%), with an average time to mortality of 31.6 days.

Preoperative blood analysis results, displayed in Table IV, reveal renal function impairment in 9 out of 25 patients (36%) and impaired liver function in 6 patients (24%) before surgery.

DISCUSSION

Mucormycosis is a fungal infection caused by filamentous Zygomycetes which predominantly invade blood vessels by Mucorales (Rhizopus, Lichtheimia, Mucor and Cunninghamella) (7). The pathogen initially buds within the paranasal sinus and can grow into the orbit or intracranially in immunocompromised patients (8). The most prevalent type of mucormycosis is rhino-orbito-cerebral, caused by Rhizopus arrhizus. Infection caused by mucormycosis may present with various symptoms including nasal congestion, runny nose, headache, nasal discharge, facial swelling, fever, visual impairment, cranial nerve palsies, and sepsis (9). Our study revealed rhino-cerebral mucormycosis as the most common type, afflicting 12 (48%) out of all patients. Eye pain (60%) and eye swelling (48%) were the most prevalent symptoms.

Table IV: Preoperative Blood Analysis of Patients

Variable	Mean ± SD
Pre-operative HbA1c values (%)	12.02 ± 3.51
Pre-operative blood sugar (mg dL^{-1})	159.01 ± 70.05
D-dimer (mg L^{-1})	1.58 ± 1.02
Fibrinogen (g L^{-1})	6.14 ± 2.26
Prothrombin Time (sec)	13.1 ± 1.76
Partial Thromboplastin Time (sec)	26.6 ± 10.37
INR	1.15 ± 0.15
Hemoglobin (g dL^{-1})	10.9 ± 2.28
White Blood Cells (x10^9 L^{-1})	12.7 ± 7.75
Platelet Count (x10^9 L^{-1})*	320 (min:29 max:885)
Neutrophils (x10^9 L^{-1})	10.6 ± 7.53
Ferritin (µg mL^{-1})	583.82 ± 393.02
C-reactive protein (mg L^{-1})*	0.22 (min:0.01 max:323)
Alanine aminotransferase (U L^{-1})*	19 (min:5 max:171)
Aspartate Aminotransferase (U L^{-1})*	24 (min:5 max:70)
Total protein (g dL^{-1})	52.95 ± 7.58
Albumin /globulin ratio	1.31 ± 0.35
Alkaline Phosphatase (U L^{-1})*	148 (min:61 max:1092)
Urea (mg dL^{-1})	43.68 ± 29.31
Creatinine (mg dL^{-1}) *	0.93 (min:0.36 max:9.56)
Calcium (mg dL^{-1})	9.06 ± 0.78
Sodium (mEq L^{-1})	133.88 ± 6.25
Potassium (mEq L^{-1})	3.69 ± 0.74
Uric Acid (mg dL^{-1})	4.15 ± 1.98

*Data not conforming to normal distribution are indicated with median and min max values.

Mucormycosis is not contagious and there is no documented evidence of human-to-human transmission. The management of this condition typically involves a combination of surgical debridement of necrotic tissues along with long-term antifungal therapy. A key aspect of preventing further progression of the disease is to manage underlying predisposing factors such as diabetes, ketoacidosis, and the use of corticosteroids and immunosuppressants (5).

The key to successful control of mucormycosis is early and aggressive surgical resection combined with early, high-dose systemic antifungal therapy. Antifungal therapy should be initiated with amphotericin B, posaconazole, or isavuconazole, but concerns related to nephrotoxicity can be minimized using saline infusion. The most frequently observed side effects associated with amphotericin B are hypokalemia, hypomagnesemia, fever, shivering, hypotension, and dyspnea (10). In patients with QTc prolongation, posaconazole should be used with caution (5). The most commonly used antifungal treatment in our study was amphotericin-B. Six patients with chronic kidney disease had elevated creatinine values. Two patients without prior chronic kidney disease experienced amphotericin-B-induced nephrotoxicity.

Comorbidities are often present in patients with mucormycosis. According to a meta-analysis of case reports, diabetes mellitus was reported as the most common underlying condition, accounting for 40% of cases (11). Since many patients with mucormycosis also have uncontrolled diabetes mellitus, managing blood glucose in the perioperative period may be difficult. This may require the use of glucose-insulin buffered solutions, insulin infusions, or intermittent insulin bolus administrations. Care must be taken to prevent hypoglycemia. Diabetes mellitus is a widely known risk factor for cardiac events during the perioperative period. Patients with diabetes mellitus often have coronary heart disease, diabetic nephropathy, autonomic neuropathy, and an increased risk for surgical site infections. In our study, 20 patients (80%) had a history of diabetes mellitus, with a mean HbA1c value of 12.02%. In these patients, perioperative insulin was administered.

Managing the airway of patients with mucormycosis can pose challenges. Fungal involvement in the oropharyngeal area and supraglottic edema can impede mask ventilation and endotracheal intubation (12). Facial edema and perioral wounds can compromise proper mask ventilation. In addition, jaw erosion and pain can limit mouth opening. Palatal ulcers can bleed when touched, and perforations in the palate can make laryngoscopy difficult (13). Thus, preanaesthetic preparation for a difficult airway is recommended. This includes having properly-sized facemasks, intubating stylets, gum elastic bougie, supraglottic devices, videolaryngoscopes, rigid laryngoscopes with varying blade sizes, and emergency tracheostomy available in the operating theater. Preoxygenation is essential (10,14). In our study, 2 (8%) patients with rhinocerebral and facial cutaneous mucormycosis had difficulty in intubation. They were managed with videolaryngoscopy and gingival elastic bougie. A tracheostomy was initially performed under sedoanalgesia due to a submandibular mass present in one patient.

Managing anesthesia for a COVID-19 patient suffering from mucormycosis poses a challenge. COVID-19 pneumonia reduces pulmonary compliance, similar to restrictive lung disease caused by fibrosis, leading to decreased functional residual capacity and diffusion capacity. Patients suffering from these conditions experience faster desaturation and are also expected to present with a difficult airway related to mucormycosis. Therefore, ensuring proper preoxygenation is essential. If bag-mask ventilation is difficult because of facial pain, a low dose of opioids is recommended (15).

Studies have revealed that perioperative COVID-19 infection leads to a 20-25% increase in mortality rates and postoperative pulmonary complications (16). It is possible that patients may be treated with steroids, anticoagulants, and anti-inflammatory monoclonal antibodies to manage their symptoms (17). COVID-19 also causes new onset diabetes mellitus in about 20.6% of patients while potentially worsening pre-existing diabetes mellitus or diabetic ketoacidosis (DKA). According to Hoenigl et al., diabetes mellitus accounts for 80% of the cases, with concomitant DKA present in 15-41% of patients who have a median HbA1c level of 11% (17). Among the COVID-19 patients in our study, 4 (66.7%) patients had diabetes mellitus with a mean HBA1c level of 9.83. Optimal glucose control with intravenous insulin during the perioperative period is critical. Due to small sample size of patients, a comparison between COVID-19 and non-COVID-19 patients was not performed in our study.

Mucormycosis is a frequently life-threatening infection. According to a review of 929 published cases of mucormycosis, the overall mortality rate was 54% (18). A retrospective cohort study examining clinical records of COVID-19-associated opportunistic fungal infections in 390 patients reported an overall mortality rate of 40.25% for COVID-19-associated mucormycosis after one year of follow-up (19). Another review noted that the total mortality rate for all types of mucormycosis ranged from 40% to 80% (20). In our study, five out of six COVID-19 patients (83.3%) died. Elevated D-dimer levels are related with increased risk of severe morbidity and mortality in COVID-19 patients. Studies have shown an increase in D-dimer levels in COVID-19-associated mucormycosis. In our findings, we also observed elevated preoperative D-dimer levels.

Patients with mucormycosis may present in a septic state, potentially due to low oral intake leading to dehydration, as well as the possibility of hypotension related to the chronic use of steroids, and subsequent adrenal suppression (13). These patients are particularly susceptible to developing hypotension during the perioperative period. Therefore, it is crucial to maintain hemodynamic stability and ensure adequate renal perfusion to prevent the progression of renal damage. Arterial cannulation is necessary to continually monitor arterial blood pressure and obtain arterial blood gas samples in unstable patients during the perioperative period (14). Two of our patients (8%) exhibited inadequate hemodynamic stability intraoperatively and required inotropes, resulting in invasive arterial cannulation.

Postoperative ICU management is crucial due to the presence of coexisting conditions and rapid infection progression (14). One review reported that 28% of patients required postoperative mechanical ventilation due to extensive surgery (5). In our study, 6 (24%) patients could not be extubated and were transferred to the ICU with an endotracheal tube. Of the patients, eleven (44%) required mechanical ventilation in the ICU. Some patients underwent extensive oral and nasal surgeries, and their airway patency could only be achieved by endotracheal tube placement.

The study's limitations include its retrospective nature and reliance on anesthesia and hospital records. The time interval between the diagnosis of mucormycosis and surgical debridement, likely to effect the success of debridement and mortality rates, was not recorded in the files. Additionally, the mortality rate might have been different if long-term follow-up had been included in the study.

Surgery on patients with mucormycosis presents perioperative anesthetic challenges such as difficult mask ventilation, intubation, kidney injury, hypotension, hemodynamic instability, inotrope requirements, maintenance of glucose levels, electrolyte balance, drug interactions, and the need for postoperative ICU management. Anticipation and preparation by anesthesiologists are crucial for a successful outcome. A multidisciplinary team, including the departments of internal medicine, infectious diseases, ear, nose, and throat surgery, and anesthesia, should collaborate to ensure safe anesthesia.

AUTHOR CONTRIBUTIONS

Conception or design of the work: BT, EE
Data collection: BC, FC, AIY, SK
Data analysis and interpretation: SK, BT, YA
Drafting the article: BT, YA
Critical revision of the article: BT, EE
The author (BT, YA, SK, AIY, FC, BC, EE) reviewed the results and approved the final version of the manuscript.

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