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REVIEW DERLEME

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COVID-19, Anesthesia and Liver: Traditional Review

COVID-19, Anestezi ve Karaciğer: Geleneksel Derleme

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ABSTRACT In the coronavirus disease-2019 (COVID-19) pandemic, which started in 2019 and was caused by the severe acute respiratory syndrome-coronavirus-2 virus, the clinical course of the infection was observed in a wide range from very mild symptoms to death. Although the respiratory system and lungs are mostly affected in COVID-19 infection, other organs and systems are also affected. The most common symptoms in COVID-19 are fever, cough, fatigue, difficulty breathing, anosmia, and loss of taste. In cases where clinical symptoms are more severe, acute respiratory distress syndrome, cytokine storms, multiple organ failure, sepsis and thrombosis are seen. Liver involvement has an important place in the course of COVID-19 apart from lung involvement, some patients with COVID-19 infection and cooperation difficulties require general anesthesia during computed tomography imaging procedures or intensive care treatments. Again, the need for urgent surgical intervention during infection causes them to be exposed to general anesthetics. The negative effects of general anesthesia agents on organ systems, especially on the liver, is an important issue that is frequently emphasized in the literature. Liver enzymes should be monitored in the clinical follow-up and estimation of mortality in patients with a diagnosis of COVID-19. Non-emergency surgeries of patients with a diagnosis of COVID-19 should be postponed or if anesthesia applications are necessary, non-hepatotoxic or minimally hepatotoxic methods should be performed. In this review, it is aimed to share information on anesthesia applications in terms of COVID-19 and liver functions by examining the relationship of COVID-19 with the liver.

Keywords: COVID-19; anesthesia; liver

ÖZET 2019 yılında başlayan, şiddetli akut solunum sendromu-koronavirüs-2 virüsünün etken olduğu koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] pandemisinde, enfeksiyonun klinik seyri çok hafif belirtilerden ölüme varan geniş bir yelpazede izlenmiştir. COVID-19 enfeksiyonunda daha çok solunum sistemi ve akciğerler etkilenmekle birlikte, diğer organ ve sistemler de etkilenmektedir. COVID-19'da en sık görülen semptomlar ateş, öksürük, yorgunluk, nefes almakta zorluk, anosmi ve tat alma duyusunda kayıptır. Klinik belirtilerin daha ağır seyrettiği olgularda ise akut solunum sıkıntısı sendromu, sitokin fırtınaları, çoklu organ yetersizliği, sepsis ve trombozlar görülmektedir. COVID-19 seyrinde solunum sistemi ve akciğer dışı organ hasarlarında karaciğer tutulumu önemli bir yer tutmaktadır. COVID-19 enfeksiyonu geçiren ve uyum sorunu olan bazı hastalara bilgisayarlı tomografi görüntüleme işlemleri ya da yoğun bakım tedavileri sırasında genel anestezi uygulamaları gerekmektedir. Yine enfeksiyon sırasında acil cerrahi müdahale gerekmesi genel anesteziklere maruz kalmalarına neden olmaktadır. Genel anestezi ajanlarının organ sistemleri üzerine, özellikle de karaciğer üzerine olumsuz etkileri literatürde sıklıkla vurgulanan önemli bir konudur. COVID-19 tanılı hastaların klinik takibinde ve mortalite tahmininde karaciğer enzimleri izlenmelidir. COVID-19 tanılı hastaların acil olmayan cerrahileri ertelenmeli, anestezi uygulamaları hepatotoksik olmayan ya da en az hepatotoksik olan yöntemlerle yapılmalıdır. Bu derlemede, COVID-19'un karaciğer ile ilişkisi irdelenerek, COVID-19 ve karaciğer fonksiyonları açısından anestezi uygulamaları konusunda bilgi paylaşılması amaçlanmıştır.

Anahtar Kelimeler: COVID-19; anestezi; karaciğer

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), can progress in a wide clinical spectrum ranging from minimal influenza symptoms to death.

The primary organ affected by the disease is the lungs.[1] However, in this infection there is also involvement of non-pulmonary organs such as the liver, kidney, and brain.[2] In fact, the incidence of liver involvement due to SARS-CoV-2 is high: 74.4% in

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severe cases and 43% in mild cases. Liver involvement has been reported in 58% of deaths due to COVID-19.[3]

COVID-19 AND LIVER FUNCTION TESTS

COVID-19 can affect liver function. In a study conducted on 148 infected patients, liver function tests were abnormal in 50.7% of the cases.[4] In SARS-CoV-2 infections with liver involvement, the most common laboratory finding is hypoalbuminemia, followed by increased levels of gamma-glutamyl transferase, aminotransferases, bilirubin, and alkaline phosphatase.[5] Studies have emphasized that aspartate aminotransferase (AST) rises more frequently than alanine aminotransferase (ALT), which is explained by the fact that mitochondrial proteins interact directly with the virus and cause direct liver damage.[6-9]

Liver enzymes are also elevated in COVID-19 cases with a severe clinical course.[3,10] In fact, studies have been conducted with the prediction that elevated liver enzymes may be a determining factor in mortality. For this purpose, Ding et al. reported that high AST and direct bilirubin levels at hospital admission were indicators of mortality due to COVID-19, Cai et al. reported that hepatic transaminase levels gradually increase in severe COVID-19 cases, and Hartl et al. reported that high AST and bilirubin levels in the diagnosis of COVID-19 are mortality markers, especially in the 40-69 age group.[11-13]

COVID-19 AND LIVER PATHOPHYSIOLOGY

Although it has been reported that SARS is probably the primary target for SARS-CoV-2 and its direct binding to angiotensin converting enzyme-2 receptors in cholangiocytes may cause liver damage but there is limited information about the pathophysiology of liver damage caused by direct viral cytopathic effects of SARS-CoV-2. But exaggerated immune responses, systemic inflammatory response syndrome, hypoxia-induced changes, vascular changes due to coagulopathy, and endotheliitis are reported.[14] Liver involvement may occur through cardiac congestion from right-sided heart failure and drug-induced liver injury.[3,15,16] Liver involvement has been associated with poor clinical outcomes.[17] Studies describing the microscopic changes due to liver involvement of COVID-19 are limited. Vishwajeet et al. found macrovesicular steatosis in the liver tissue, vascular changes and lobular necroinflammation, portal inflammation, and cholestasis in the autopsy of patients with a mean duration of 13 days from symptom onset to death and 9 days in the hospital, and centrizonal obstruction with ischemic hepatocyte loss in one-quarter of the cases.[18] Hammoud et al. also reported that they found 59.3% steatosis, 31.1% fibrosis, 29.6% hepatic congestion, 27.1% inflammation, 22.1% hepatic necrosis, 4% cholestasis, and 2% cirrhosis.[19] Elsoukkary et al. detected hepatic congestion in the liver, followed by central vein thrombosis, hepatic steatosis, portal fibrosis, lymphocytic infiltrates, ductular proliferation, canalicular cholestasis, and hepatocyte necrosis.[20] Similarly, Kaltschmidt et al. reported that SARS-CoV-2 infects the liver as part of the systemic disease, and they detected significant microvascular thrombotic disease and organ damage.[17] Other publications report COVID-19-related hepatic steatosis, portal fibrosis, ductal proliferation with lymphocytic infiltrates, lobular cholestasis, and acute liver cell necrosis with central vein thrombosis.[21,22]

COVID-19 AND LIVER FAILURE

When Saini et al. retrospectively evaluated 150 COVID-19 patients, they found that more than half of them had elevated liver enzyme levels, which were significantly higher in men (67.4%) than in women (46.03%) and which correlated with increasing age. They also reported that a significant portion of these patients had liver damage. Furthermore, 21.15% of patients with normal liver enzymes, 37% of patients with elevated liver enzymes, and 52% of patients with liver damage required the intensive care unit.[23]

When Hartl et al. evaluated 496 hospitalized COVID-19 patients, approximately 20% of the patients without chronic liver disease developed progressive cholestasis after SARS-CoV-2 infection, and those with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis were more likely to develop secondary sclerosing cholangitis after COVID-19. They concluded that patients are at risk for developing cholestatic liver failure and/or secondary sclerosing cholangitis after COVID-19 infection.[13] Acute liver failure due to COVID-19 is extremely rare, but may present with clinical manifestations of coagulopathy and encephalopathy within 28 days of the onset of jaundice. It has a mortality rate of 70-80% if liver transplantation is not performed.[24]

HEPATOTOXICITY OF DRUGS USED IN THE TREATMENT OF COVID-19

Although no treatment drug is 100% successful, especially during the early period of the pandemic, many drugs have been used. In the literature, antivirals such as remdesivir, nirmatrelvir/ritonavir, molnupiravir, lopinavir/ritonavir, ribavirin, darunavir, and favipiravir have been used in the treatment of COVID-19. Immunomodulator therapies such as tocilizumab, interferon α/β, and baricitinib are also used to treat COVID-19. Antiparasitic drugs including chloroquine and hydroxychloroquine have been used. Publications show that the antiparasitic options can cause liver damage.[25,26]

In cases that did not receive specific treatment, drugs were used to control the symptoms. For this purpose, acetaminophen was the most frequently chosen agent because of its antipyretic properties. It is known that acetaminophen can cause liver damage.[26,27]

ANESTHESIA OF PATIENTS DIAGNOSED WITH COVID-19

During the pandemic, some patients required anesthesia during surgical emergencies, imaging procedures, or stays in the intensive care unit, although surgery was recommended to be postponed for 7 weeks for non-emergency conditions.[28] Anesthesia-related complications are reported in fewer pediatric cases of COVID-19 than in adults.[29,30] Geng-Ramos et al. recommended that elective surgeries should be postponed for at least 28 days after the first positivity in order to reduce contagiousness and minimize anesthesia risks in asymptomatic pediatric patients.[31] Pregnant women were also susceptible to SARS-CoV infection.[32,33] Chen et al. reported that 17 pregnant women diagnosed with COVID-19 were in stable condition during pregnancy, although they had COVID-19 findings on thoracic computed tomography. They did not have preoperative ALT or AST abnormalities and completed their deliveries with an epidural or general anesthesia. The importance of neuraxial anesthesia was emphasized for reducing possible pulmonary complications.[34] On the other hand, it has also been reported that maternal COVID-19 infection in the peripartum period may cause laboratory results similar to hemolysis, elevated liver enzymes, low platelet count syndrome. Therefore, the evaluation of D-dimer, prothrombin time, platelet count, activated partial thromboplastin time (APTT), and fibrinogen may be appropriate.[35]

Furthermore, delayed diagnosis of patients with COVID-19 causes high morbidity and mortality, and patients may present with acute abdomen secondary to gallbladder perforation.[36]

The pandemic has limited liver transplant programs. Current guidelines recommend deferring liver transplantations planned for another reason in patients with severe SARS-CoV-2 infection until clinical recovery from the infection occurs and 2 polymerase chain reaction tests collected at least 24 hours apart are negative.[37]

RELATIONSHIP BETWEEN SURGERY AND COVID-19

According to an international multicenter study, in cases with COVID-19, a significant relationship was found between being over 70 years old, being in the American Society of Anesthesiologist III-V risk group, presence of malignant disease, undergoing emergency and major surgery, male gender, and incidence of death within 30 days after surgery.[38]

RELATIONSHIP BETWEEN ANESTHESIA AND LIVER FUNCTIONS

Liver damage by drugs is not so rare. The relationship between hepatic function and anesthesia is an issue that is taken into account in daily anesthesia practice.

While acute and chronic liver dysfunctions may impair the response to anesthesia and surgery, some anesthetic agents and hemodynamic deterioration may also lead to significant hepatic dysfunction in the postoperative period. Minimal elevations (<2X) in liver enzymes do not require the operation to be postponed if there are no other features in the physical examination and history. However, higher elevations or accompanying elevations in bilirubin require further evaluation and investigation.[39]

The pathogenesis of COVID-related coagulopathy is not yet known, and coagulopathy resulting from "thromboinflammation" becomes evident with increased D-dimer and fibrinogen levels, minimal changes in prothrombin time, APTT and platelet count. Bleeding findings are not common despite coagulopathy.[40] Fresh frozen plasma and/or cryoprecipitate are sufficient to correct coagulopathy in patients with acute and chronic liver failure. Treatment should be arranged according to the analysis of the international normalized ratio, plasma fibrinogen level, and, if possible, specific coagulation factors. Furthermore, a thromboelastogram should be used for monitoring.[41,42]

Hypotension, bleeding, and the use of vasopressor agents may impair hepatic oxygen delivery. Positive pressure ventilation and positive end-expiratory pressure can also increase venous pressure, resulting in a decrease in cardiac output and total hepatic blood flow. Hyperventilation should be avoided because hypocarbia reduces hepatic blood flow.[41-44]

Many studies evaluate the hepatotoxic properties of fluorinated hydrocarbons used in general anesthesia. The rates of cytochrome P450-dependent metabolism are 20%, 2-5%, 0.2-0.6%, and 0.02% for halothane, isoflurane, sevoflurane, and desflurane, respectively.[45] In addition to its toxic effects on the liver, halothane also impairs hepatic hemodynamics.[46] Severe halothane hepatitis is seen in 1/6,000-1/35,000 patients administered halothane. Although repetitive applications are generally blamed, it has been reported even in the case of first exposure to a volatile anesthetic (39%).[47] While the hepatotoxicity of sevoflurane is multifactorial, the hepatotoxicity of halogenated volatile anesthetics other than sevoflurane are related to their metabolism.[45] Although desflurane-induced hepatotoxicity has been more frequently described in adults, it has also been shown in pediatric cases.[48] However, isoflurane can be administered safely in patients with hepatic disease and it is the agent that best protects hepatic blood flow.[40,49] In multiple-dose studies with propofol, one of the intravenous anesthetics, no toxic or pathological effects on the organs were observed, its use in single or repeated doses had no effect on liver enzymes, and its potency did not cause liver dysfunction.[50,51] Therefore, it is recommended as the ideal agent of choice for the induction and maintenance of anesthesia in patients with chronic liver disease.

Since the elimination of narcotics may decrease and blood levels may increase in analgesia of patients with liver dysfunction, the dose should be carefully evaluated. In these cases, the elimination half-life of morphine increases significantly, but the metabolism of fentanyl and methadone is less affected. Remifentanil, which is metabolized independently of the liver, should be preferred in patients with hepatic dysfunction.[52]

Most non-depolarizing muscle relaxants are metabolized in the liver. The duration of neuromuscular block is prolonged in hepatic failure. The liver plays an important role in the metabolism of steroidal muscle relaxants, especially vecuronium and rocuronium. In addition, in hepatic failure, the initial dose requirement is higher due to increased distribution volume, but repeat doses should be reduced due to decreased plasma clearance. Since their elimination is not in the liver, atracurium or cisatracurium should be preferred as muscle relaxants in patients with hepatic/renal failure or multi-organ failure.[53]

In patients diagnosed with COVID-19, precautions should be taken for the safety of other patients and healthcare workers, as well as the patient's own safety.[54]

Ketamine is a frequently preferred agent in sedation procedures, but one of the most common side effect is increased oral and bronchial secretions.

Suri et al. drew attention to the following issues regarding ketamine; 1) Preserved gag and cough reflex during procedural sedation can increase the aerosol spread, 2) Increase in the amount of aerosol generated from saliva and bronchial secretions caused by leaks around the endotracheal tube cuff in a patient on positive pressure ventilation, 3) Repeated oral and bronchial suctioning increases the healthcare worker exposure, and repeated suctioning also carries an inherent risk of aerosolization of the virus particles, 4) Blurring of vision of videolaryngoscope.[55]

CONCLUSION

In conclusion, since SARS-CoV-2 is a disease that can involve the liver, liver function should also be monitored in the clinical follow-up of the patients and in the estimation of mortality. The hepatotoxicity of the drugs used for the treatment and the liver failure occurring during the course of the disease should be taken into consideration. Non-emergency surgeries of patients with a diagnosis of COVID-19 should be postponed and anesthesia applications should be performed with non-hepatotoxic or the least hepatotoxic methods.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Ayşe Hande Arpacı, Berrin Işık; **Design:** Ayşe Hande Arpacı, Berrin Işık; **Control/Supervision:** Berrin Işık; **Data Collection and/or Processing:** Ayşe Hande Arpacı; **Analysis and/or Interpretation:** Ayşe Hande Arpacı, Berrin Işık; **Literature Review:** Ayşe Hande Arpacı; **Writing the Article:** Ayşe Hande Arpacı, Berrin Işık; **Critical Review:** Berrin Işık.*

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