Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Xu Chen[1,3]
Shen Chen[2]
Juan Pang[1]

Yi Tang[1]
Wenhua Ling[1,3,*]
[1]*Department of Nutrition, School of Public Health, Sun Yat-Sen University, Guangzhou, People's Republic of China*
[2]*Department of Toxicology, School of Public Health, Sun Yat-sen University, Guangzhou, People's Republic of China*
[3]*Guangdong Provincial Key Laboratory of Food, Nutrition and Health, Guangzhou, People's Republic of China*
[*]Corresponding author. Address: School of Public Health, Sun Yat-Sen University (Northern Campus), No.74, 2nd Zhongshan Road, Guangzhou, P.R. China 510080, Tel.: 86-20-87331597; Fax: 86-20-87330446.
E-mail address: lingwh@mail.sysu.edu.cn (W. Ling)

Progressive cholangiopathy in COVID-19 patients: Other possible diagnoses than ketamine-induced cholangiopathy should be considered

To the Editor:

We read with great interest the article by Mallet *et al.* on several cases of cholangiopathies occurring in patients with COVID-19.[1] The authors hypothesized that use of ketamine led to biliary lesions due to precipitations of norketamine, a water-insoluble by-product produced in the liver by nitrogen demethylation. In addition to a potential ketamine-induced toxicity we postulate than vascular lesions may have contributed to the observed biliary lesions.

More specifically, arterial injuries supplying the bile ducts may result in ischemic lesions.[2] Several lines of arguments support this hypothesis. First, all patients required mechanical ventilation for a long time (median: 40 days), a feature commonly observed in severely ill patients suffering from ischemic cholangiopathy.[3,4] An inspired oxygen fraction greater than 80% and lung protective mechanical ventilation (low tidal volume, prone positioning, high positive end-expiratory pressure) are known to lower splanchnic blood flow. Whether patients required such measures was not reported by Mallet *et al.* Second, all patients received high doses of vasopressors which further reduced splanchnic blood flow.[4,5] Third, the use of high doses of vasopressors implies severe hemodynamic instability as it has been observed in most of the patients with ischemic cholangiopathy occurring after a prolonged stay in intensive care. It is likely that this phenomenon compromised the blood supply to many organs including the bile ducts.[5] Lastly, the lesions observed in the patient who underwent endoscopic retrograde cholangiopancreatography revealed contrast medium filling defects in the common bile duct and rarefication of the intrahepatic biliary tract, a feature often observed in patients suffering from ischemic cholangiopathy following liver transplantation.[6]

Cholangiopathy occurring after a prolonged stay in intensive care has been identified only in recent years. We believe that this pathophysiological mechanism is a plausible explanation for biliary lesions observed in patients with COVID-19.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

Pierre Deltenre: study design; drafting the manuscript; critical revision of the manuscript for important intellectual content; study supervision. Christophe Moreno: critical revision of the manuscript for important intellectual content. Eric Trépo: critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.02.036.

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Pierre Deltenre[1,2,*]
Christophe Moreno[1,3]
Eric Trépo[1,3]

[1]*Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium*
[2]*Department of Gastroenterology and Hepatology, Clinique St Luc, Bouge, Belgium*
[3]*Laboratory of Experimental Gastroenterology, Université Libre de Bruxelles, Brussels, Belgium*
[*]Corresponding author. Address: Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.
E-mail address: pierre.deltenre01@gmail.com (P. Deltenre)

Reply to: "Progressive cholangiopathy in COVID-19 patients: Other possible diagnoses than ketamine-induced cholangiopathy should be considered"

Intravenous ketamine is a risk factor for jaundice in COVID-19 patients

To the Editor:

In their reply to our initial report[1] Deltenre, Moreno and Trepo[2] postulated that vasculobiliary injuries could have contributed to our cases of COVID-19 cholangiopathies, which is, undeniably, a possibility. However, critical care vasculobiliary injuries are associated with haemodynamic instabilities and hepatic ischemia. In our series, the maximum serum lactate level remained below 2.5 mmol/L in 3 out of 5 patients, which rules out shock and tissue (including hepatic) hypoperfusion. In another series of 12 patients with COVID-19 cholangiopathy, 2 (16.7%) patients never received vasopressors.[3] Therefore, we think that vasculobiliary injuries are not the only causes of COVID-19 cholangiopathies, and that multiple hits, including drug injury, and maybe SARS-CoV-2 toxicity, could account for the syndrome. At the time of writing, 24 patients with COVID-19 cholangiopathy have been reported in the literature. The common point was mechanical ventilation. Maintenance sedation with ketamine was reported in 10 (41.7%) patients.[1,4,5] Otherwise, the maintenance sedation protocol was unmentioned.

We investigated, after our initial observations, the relationship between hospital consumption of ketamine and maximum total serum bilirubin level of patients who underwent mechanical ventilation for COVID-19 in 15 adult hospitals of the Assistance Publique — Hôpitaux de Paris (AP—HP). Health data and drug consumptions were collected from the AP—HP health— (NB, MD) and central pharmacy— (VS, MT) datawarehouses. Sedative drug consumption, including ketamine, midazolam, and propofol, were estimated by hospital and by COVID-19 patient, and categorized as >median ("higher") and ≤median ("lower") drug consumptions. The sample comprised 2,258 (mean [SD] age 60 [13]; 73% men) patients. Their characteristics, overall, and by ketamine consumption are presented in Table S1. Patients in the lower ketamine group were older (p = 0.043), and were more severe, in terms of comorbidities (p <0.001) and initial serum C-reactive protein level (p = 0.045). Sex, maximum serum creatinine level, and mortality were similar between the lower and higher ketamine patient group. The mean (SD) maximum total serum bilirubin level was 19 (24) and 17 (20) μmol/L in the higher and lower ketamine groups, respectively (p = 0.016). Other surrogates of the intensive care effort, including higher consumptions of midazolam (p = 0.025) and of propofol (p = 0.62), were not associated with higher levels of total serum bilirubin (Fig. 1). Therefore, ketamine was associated with jaundice in this cohort. Whether ketamine-associated jaundice contributed, or not, to organ failure is unknown and should be investigated. The guidelines for maintenance sedation of patients with acute respiratory distress syndrome (ARDS), regardless of COVID-19, include ketamine as a second-line agent. We think that clinicians should refrain from using ketamine to sedate patients with ARDS, including those with COVID-19. If cornered into such a prescription, ketamine should only be used short-term, and bilirubin should be closely monitored.

Keywords: Ketamine; Cholestasis; Intrahepatic; Cholangiopathy; Cholangitis; COVID-19; Chemical and Drug Induced Liver Injury.
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