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Potential role of ketamine in burn-associated cholestasis

To the Editor:

We read with interest the paper by de Tymowski *et al.*[1] describing the factors and outcomes of burn-associated cholestasis. This retrospective study described 111 patients (52%) with burn-associated cholestasis among 214 patients who had suffered severe burn injuries.

The authors suggested that increased levels of total bilirubin ≥2x the upper limit of normal (ULN) with or without an increase in serum alkaline phosphatase (ALP) ≥1.5x the ULN or gamma-glutamyltransferase (GGT) ≥3x the ULN was associated with poorer survival at 90 days. Of the 74 patients alive at the time of discharge from the intensive care unit (ICU), 38 had cholestasis. As the authors describe, biliary lesions in severe burn injuries may be related to hypoxic hepatitis or hypovolemic shock.

We report the case of a 29-year-old man admitted to our ICU for burns following a road traffic accident. On Day 17 after admission, he developed icteric cholestasis: aspartate aminotransferase: 79 UI/L, alanine aminotransferase: 69 UI/L, GGT: 551 UI/L, ALP: 332 UI/L, prothrombin time: 62%, total bilirubin: 27 μmol/L. Bilirubin increased to more than 25x the ULN over a 3-month period. Viral hepatitis, autoimmune hepatitis, obstructive jaundice, and alcoholic hepatitis were ruled out. A liver biopsy showed cholangitis without fibrosis or steatosis, and magnetic resonance cholangiography was normal. The only potentially incriminating drug was ketamine administered for analgesia (between 200 mg and 400 mg daily for more than 3 months). When ketamine was stopped, icteric cholestasis gradually improved over several months.

Ketamine is a commonly used dissociative anesthetic that antagonizes the N-methyl-D-aspartate (NMDA) receptor. At subanesthetic doses it has strong analgesic properties that can be beneficial for neuropathic pain resistant to conventional therapies.

An association between ketamine use and chronic cholangiopathy was first described in drug users, and several case series have been published showing cholestasis in regular recreational users of ketamine.[2–6] Typically, when ketamine is stopped, the cholestasis gradually resolves. The pathological abnormality described in these patients is main bile duct dilation without obvious obstructing biliary lesions. Several mechanisms were mentioned, the induction of persistent sphincter of Oddi spasm leading to biliary obstruction and the stimulation of the NMDA receptor in the smooth muscle cells of the bile duct that could induce inflammation, fibrosis and finally strictures.[6,7]

Maintaining adequate analgesia in patients with severe burn injuries is a challenging problem, especially during wound care procedures. Ketamine is regularly used and preferred to morphine because it does not depress respiration. Although an association between ketamine use and liver injury is described,[8] proving causality is much more difficult.

We are therefore interested to know if any patients in the study by de Tymowski *et al.*[1] received ketamine and whether spontaneous regression of cholestasis could be related to discontinuation of ketamine.

Moreover, urinary tract dysfunction was reported in up to 30% of active ketamine users due to direct epithelial damage or microvascular injury caused by toxic metabolites.[9] We are also interested to know if cases of urinary tract dysfunctions, potentially related to ketamine use, were reported in this cohort of patients with burn-associated cholestasis.

Data supporting ketamine-induced chronic cholangiopathy would challenge the use of ketamine in burns patients developing cholestasis. Awareness of this association highlights a potential reversible cause of cholestasis.

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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

All authors drafted and approved the final manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.009.

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