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LETTER

Role of intravenous ketamine in the pathogenesis of secondary sclerosing cholangitis in critically ill patients: perpetrator or innocent bystander? Answers provided by forensic toxicology

Silke Leonhardt[1], Sven Baumann[2], Christian Jürgensen[3], Lars Hüter[4] and Julia Leonhardt[5*] on behalf of the Ketamine Cast Research Group

Dear Editor,

We read with great interest the article by de Tymowski et al. highlighting the role of ketamine in the pathogenesis of secondary sclerosing cholangitis in critically ill patients (SSC-CIP) [1]. They suggest that the biliary casts observed in patients with SSC-CIP associated with coronavirus disease 2019 (COVID-19) correspond to biliary precipitations of norketamine, the active metabolite of ketamine. Norketamine precipitation in bile ducts could represent a crucial step in the pathogenesis of SSC-CIP, the Keta-Cov Research group speculated [1, 2]. There is no doubt that clarifying such potentially harmful effects of ketamine is of immense clinical relevance for intensive care medicine.

To move beyond speculation, we tested this hypothesis. We made the following assumptions (based on the Bradford Hill criteria for causation) [3]:

1. If the precipitation of norketamine and/or ketamine was a crucial step in the pathogenesis of cast formation and SSC-CIP, all casts should contain norketamine and/or ketamine (consistency of association).
2. If there was a causal relationship between ketamine exposure and SSC-CIP development, the exposure must occur prior to the disease onset (temporality).

Biliary casts of ten critically ill patients with confirmed SSC-CIP were examined for ketamine and its metabolites by means of forensic toxicological analyses (Fig. 1). During their stay in the intensive care unit (ICU), all patients had received intravenous ketamine starting at a median of 3.5 [interquartile range (IQR) 1.0–11.8] days after intubation. Endoscopic retrograde cholangiography (ERC) was performed in our patients for diagnosis and treatment of SSC-CIP [4]. During ERC, the casts were removed from the bile ducts (with a balloon, basket or forceps) and preserved in sterile water. The dimensionally stable casts were then examined using liquid chromatography coupled to mass spectrometry-based approaches (see supplementary material for detailed methods).

The test method was able to detect ketamine and its metabolites in the extracted casts, demonstrating its appropriateness (Supplementary Table 1). With a detection limit of 0.07 pg/mg for ketamine, the method was highly sensitive. Intravenously administered ketamine is biotransformed into norketamine (metabolite I), which is in turn converted by CYP2A6 and CYP2B6 into hydroxynorketamine and dehydronorketamine (metabolite II). Ketamine and its metabolites are

*Correspondence: julia.leonhardt@med.uni-jena.de
[5] Department of Anesthesiology and Intensive Care Medicine, University Hospital Jena and Center for Sepsis Control and Care, University Hospital Jena, Am Klinikum 1, 07747 Jena, Germany
Full author information is available at the end of the article

Silke Leonhardt and Sven Baumann contributed equally to this work.

The members of Ketamine Cast Research Group are listed in the Acknowledgement Section.

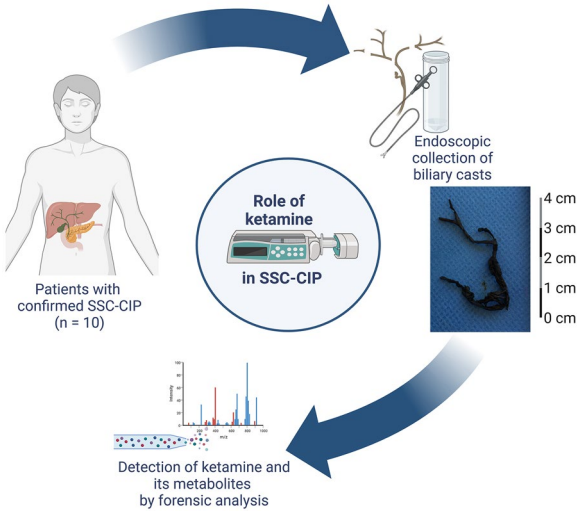

Fig. 1 Biliary casts from ten patients with SSC-CIP were removed during endoscopic retrograde cholangiography (ERC) and analyzed for the presence of ketamine and its metabolites. The figure was created with BioRender.com

partially excreted into the bile [5]. The results of our toxicological analyses are presented in Supplementary Table 1. In most of our patients, traces of either ketamine and/or its metabolites could be semi-quantitatively detected in the biliary casts or in the surrounding solution (8/10 patients). However, the quantities of ketamine and/or ketamine metabolites in the casts were small, reaching a maximum of 181 pg/mg. This corresponds to a mass fraction of < 0.0001%. Ketamine and its metabolites are generally accepted as very stable molecules with no or only marginal spontaneous degradation even after months [6–9]. Although no study of ketamine stability in biliary casts exists, a large body of evidence demonstrates its high stability in different fluids and under various conditions [6–9]. Therefore, the negligible content of ketamine in the biliary casts is more suggestive of ketamine/norketamine admixture to the casts than of a precipitation.

Bound within casts, ketamine and norketamine apparently remain in the bile ducts for a very long time. In one case, traces of norketamine were still detectable within a cast 274 days after ketamine medication. Interestingly, the patient with the shortest ketamine use had the highest ketamine concentration in the cast. Conversely, no ketamine or metabolites could be detected in two cases, although the patients had been treated with ketamine (negative for consistency of association). This means that biliary casts can form in the absence of ketamine, i.e., ketamine is not a *conditio sine qua non*. The fact that some patients (4/10) had already developed cholestasis (as the first sign of bile duct destruction) before the first dose of ketamine was administered (negative for temporality) supports this conclusion. Although ketamine could be involved in some way, the hypothesis that ketamine is the main perpetrator in the pathogenesis of biliary cast formation and SSC-CIP cannot be confirmed by our data. In addition, biliary casts contained admixtures of the following drugs that had been administered during the ICU stay: ciprofloxacin, trimethoprim, midazolam, metoclopramide, metoprolol, amiodarone, 7-hydroxyquetiapine, quetiapine, 4-aminoantipyrine, noramidopyrine, hydromorphone, dioxoprothazine, pipamperone, melperone, haloperidol, butylscopolamine, diatrizoate, promethazine, lidocaine and mirtazapine.

Nevertheless, the forensic methods used here allow scientifically verifiable insights into the pathogenesis of SSC-CIP for the first time. Due to their immense stability, biliary casts represent a record of the biliary excretions during the time of cast formation, thus a "look into the past" is possible. If the casts contain ketamine, they must have formed or have been present at the time of ketamine administration. Since in individual patients of our series, ketamine administration stopped on the 7th, 11th or 15th ICU day, the casts must have been developed very early, within the first 7–14 days in the ICU. This provides indirect proof of the very early destruction of the bile ducts with cast formation in SSC-CIP and dispels the old belief that the SSC-CIP exclusively occurs after long-term intensive care treatment.

The exact explanation for the association between ketamine and SSC-CIP, however, needs to be further elucidated.

Supplementary Information
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Author details
[1] Department of Hepatology and Gastroenterology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. [2] Department of Forensic Toxicology, Institute of Legal Medicine, University of Leipzig, Johannisallee 28, 04103 Leipzig, Germany. [3] Department of Hepatology and Gastroenterology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Campus Charité Mitte, Charitéplatz 1, 10117 Berlin, Germany. [4] Department of Anesthesiology and Intensive Care Medicine, Klinikum Frankfurt/Oder GmbH, Müllroser Chaussee 7, 15236 Frankfurt (Oder), Germany. [5] Department of Anesthesiology and Intensive Care Medicine, University Hospital Jena and Center for Sepsis Control and Care, University Hospital Jena, Am Klinikum 1, 07747 Jena, Germany.

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Ketamine Cast Research Group: Lisa Höfert, Department of Forensic Toxicology, Institute of Legal Medicine, University of Leipzig, Johannisallee 28, 04103 Leipzig, Germany. Michael Bauer, Department of Anesthesiology and Intensive

Care Medicine, University Hospital Jena and Center for Sepsis Control and Care, University Hospital Jena, Am Klinikum 1, 07747 Jena, Germany. Frank Tacke, Department of Hepatology and Gastroenterology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Campus Virchow Klinikum, Augustenburger Platz 1, 13353, Berlin, Germany and Department of Hepatology and Gastroenterology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Campus Charité Mitte, Charitéplatz 1, 10117, Berlin, Germany.

Author contributions
SL and JL designed the study and drafted the manuscript, SL and CJ collected the casts, SB and L. Höfert carried out the forensic analyses, SB contributed to the manuscript, and SL and L. Hüter collected clinical data. All authors critically revised the manuscript and approved the final version.

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Declarations

Conflicts of interest
The authors have no conflict of interest pertinent to this study.

Ethics approval
The study was approved by the local ethics committee of Charité-Universitätsmedizin Berlin (EA2/066/20 and EA/129/20). The patients or their legal representatives had given their written consent to participate in the study.

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