Research Article

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Statin therapy is associated with reduced incidence of hypoxic hepatitis in critically ill patients

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Background & Aims: Hypoxic hepatitis (HH) is a frequent and life-threatening complication associated with states of oxygen depletion in critically ill patients. Ischemia and reperfusion contribute to liver injury in HH. Experimental data suggest beneficial effects of statins in hepatic ischemia/reperfusion injury. This study was conducted to investigate whether statin treatment prior to intensive care unit (ICU) admission affects incidence rates and severity of HH.

Methods: Eight hundred fifty-one patients admitted consecutively to three medical ICUs between December 2008 and December 2009 were prospectively screened for new occurrence of HH within 48 h following ICU admission. Statin treatment prior to ICU admission was assessed. 28-day-, 90-day-, and 1-year-survival as well as new-onset of complications in HH patients were prospectively documented.

Results: Eighty-seven patients (10%) developed HH. Statin treatment prior to ICU admission was significantly associated with decreased incidence of HH within 48 h after ICU admission in the multivariate analysis (adjusted OR = 0.42 (95% CI 0.19–0.95); p <0.05). Cardiogenic shock (p <0.001), septic shock (p <0.001) and active alcohol consumption (p <0.01) were identified as independent risk factors for development of HH. 28-day-, 90-day-, and 1-year-mortality rates in HH were 58%, 67%, and 74%, respectively. Statins were associated with improved 28-day-survival in the total study cohort (p <0.05), but did not affect 90-day- and 1-year-mortality, respectively.

Conclusions: Cardiogenic shock, septic shock, and active alcohol consumption were independent factors predisposing patients to new onset of HH. Statin treatment prior to ICU admission was the only protective factor regarding the new occurrence of HH in critically ill patients.

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Abbreviations: I/R, ischemia/reperfusion; HH, Hypoxic Hepatitis; ICU, Intensive Care Unit; SAPS II, simplified acute physiology score; SOFA, sequential organ failure assessment; ACE, angiotensin converting enzyme; AT II, angiotensin II; CPR, cardiopulmonary resuscitation; IQR, interquartile range; AMI, acute myocardial infarction; RRT, renal replacement therapy; LFT, liver function tests.

Introduction

Since their introduction in the late 1980's, 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors, commonly referred to as statins, have become one of the most frequently prescribed drugs in developed countries [1,2]. Statins are among the most potent lipid-lowering agents, and their efficacy in reducing the incidence of coronary events has been repeatedly demonstrated [3–5]. Statin use is recommended in current guidelines for treatment of hypercholesterolemia [6] and coronary heart disease [7].

Apart from their lipid-lowering capacities, statins exert pleiotropic effects that may contribute to the beneficial features. Experimental models suggest that statins improve hepatic microcirculation and endothelial function [8,9], reduce platelet recruitment [10,11], decrease vascular [12] and systemic inflammation [13], and attenuate hepatic ischemia/reperfusion (I/R) injury [14–16]. Recently, it has been shown that treatment with simvastatin attenuated lipopolysaccharide-induced hepatic sinusoidal dysfunction in rodents [9]. Additionally, simvastatin and atorvastatin attenuated hepatic injury and fibrosis following bile-duct-ligation in rats [17,18]. These experimental data indicate that statins have beneficial effects on hepatic perfusion and may have potential effects in preventing and treating ischemic liver injury.

Hypoxic hepatitis (HH), also known as shock liver or ischemic hepatitis, is a life-threatening event associated with high morbidity and mortality [19–23]. HH is characterized by diffuse hepatic injury resulting from cardio-circulatory or respiratory impairment [19,20], and its presence is suggested by a marked,

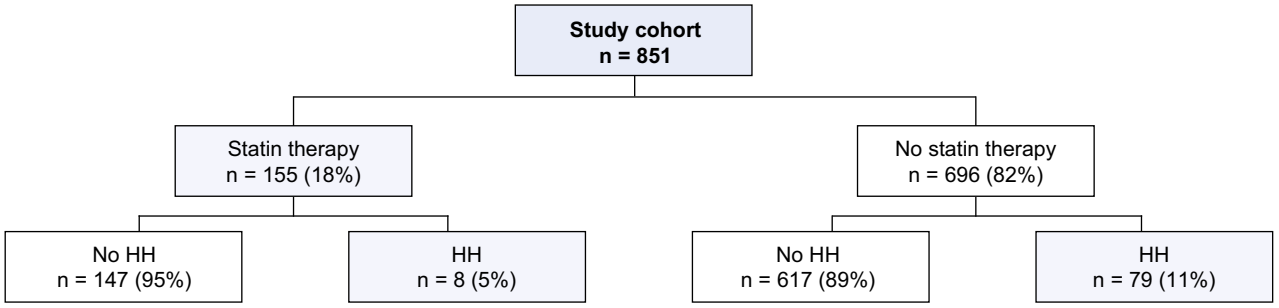

Fig. 1. Study flowchart.

transient and potentially reversible increase of aminotransferase levels in the appropriate clinical setting [19–23]. In critically ill patients at the medical intensive care unit (ICU), incidence rates of up to 11% with an ICU-mortality rate of 57% were observed [22]. Treatment of the underlying condition is currently the only therapy. As ischemia/reperfusion injury, inflammation, and endothelial/sinusoidal dysfunction are cardinal factors contributing to development of HH [24], statins may influence incidence and course of HH in critically ill patients.

Therefore, we investigated whether statin treatment prior to ICU admission affects incidence rates, severity and complications of HH in this prospective study in critically ill patients at the medical ICU.

Patients and methods

This prospective study was performed at 3 medical ICUs located at the Medical University Vienna (Vienna, Austria). All patients admitted to the 3 ICUs, between December 2008 and December 2009, were eligible for inclusion in the study. A total of 851 consecutive patients were included and studied prospectively.

All patients were prospectively screened for new onset of HH within 48 h after ICU admission. This observation window was chosen due to the reported time frame of rise of aminotransferase levels following hepatic injury [25], and due to significantly increased plasma levels and prolonged elimination half-life of statins in critical illness [26]. HH was defined according to the three following criteria [19–22]: (1) a clinical setting of cardiocirculatory and/or respiratory failure; (2) a marked but reversible elevation of aminotransferase levels to at least 20-fold the upper limit of normal; (3) exclusion of other potential causes of liver cell necrosis (e.g., drug induced or viral hepatitis). Liver biopsy is not required for the diagnosis of HH when the criteria listed above are met [19,22]. Liver cirrhosis was diagnosed in patients presenting a combination of characteristic clinical, laboratory and radiological findings [23]. Relevant alcohol consumption was defined in female patients consuming more than 1 standard-drink (10 g of ethanol [27]), and in male patients consuming more than 2 standard-drinks per day [28,29]. Binge drinking (more than 5 standard drinks on one occasion) was also considered as relevant alcohol consumption [28].

Cardiogenic shock was diagnosed as previously described [30]. Sepsis and septic shock were diagnosed according to well established criteria [31,32]. The complete medical history and medication including statin use prior to ICU admission and chronic underlying diseases were assessed via anamnesis (including third party), by contacting the attending physicians and general practitioners, and by reviewing the patients' medical records. Patients who were under statin therapy prior to ICU-admission were included in the statin-group and were compared to patients without prior statin use. A detailed study flowchart is shown in Fig. 1.

Simplified acute physiology score (SAPS II) [33] and sequential organ failure assessment score (SOFA) [34] were calculated on ICU-admission. Additionally, Charlson Comorbidity Score was calculated as previously described [35]. Laboratory analyses and hemodynamic parameters were assessed on a daily basis.

Need for vasopressors, mechanical ventilation, renal replacement therapy, artificial nutrition and blood products were documented during the stay at the ICU. ICU mortality was assessed on site; 28-day mortality, 90-day-mortality, and 1-year-mortality were assessed by contacting the patient or the attending physician, respectively.

Complications associated with HH were documented prospectively during the patients' ICU stay. Cardiopulmonary complications were categorized as new onset of acute myocardial infarction, cardio-pulmonary resuscitation (CPR), rhythmogenic events, and cardiogenic shock during follow-up. Renal complications were defined by necessity of RRT. Jaundice was defined as serum bilirubin >3 mg/dl during the ICU stay [36]). Infectious complications were diagnosed in patients with new onset of pneumonia, bloodstream infections, urinary tract infections, and soft tissue infections, following occurrence of HH [23]. Gastrointestinal complications were diagnosed in patients with mesenteric ischemia [37] during follow-up. Fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding, a decline in the hemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least 4 units of red cells were considered major bleeding complications [38]. Neurologic complications were cerebral ischemia, bleeding and herniation.

This study was approved by the ethics committee of the Medical University Vienna and was conducted in accordance with the Declaration of Helsinki and its current revision. The ethics committee waived the need for informed consent due to the observational character of this study.

SPSS Statistics 20 (IBM, Armonk, NY, USA) was used for statistical analysis. Data are presented as median (25–75% interquartile range; IQR) for metric variables or as absolute number (percentage; %). The primary aim of this study was to evaluate the association between statin treatment and occurrence of HH. Continuous variables were compared using Mann-Whitney-U test, binary variables via Chi-Square-Analysis or Fisher's exact, as appropriate. Associations of SAPS II and SOFA score, respectively, with occurrence of HH were evaluated via the area under the receiver operating characteristic curve (AUROC). Multivariate logistic regression analysis was performed to evaluate the impact of statins on HH after adjustment for potential, predefined confounders. Goodness of fit for the regression model was assessed by Hosmer-Lemeshow-Test and corrected r^2. A p value <0.05 was generally considered statistically significant.

Results

Patients' characteristics

Clinical characteristics of the total study cohort stratified to statin use are illustrated in Table 1. 851 patients were included in the study. Primary reasons for ICU admission were cardiogenic events and/or cardiopulmonary resuscitation (n = 274, 32%), infections/sepsis (n = 192, 23%), post-operative care (n = 144, 17%), respiratory insufficiency (n = 98, 11%), neurologic diseases (n = 58, 7%), bleeding (n = 25, 3%), and other (n = 60, 7%). 155 (18%) patients were on statin therapy prior to ICU admission. The most commonly used statin was atorvastatin (45%), closely followed by simvastatin (43%). Details about statin treatment including dosages are illustrated in Table 2.

Concerning most relevant other pre-medications, one hundred eighty-one patients (21%) were under ACE-inhibitor therapy, 153 (18%) had beta-blockers, 64 (8%) had calcium-channel-blockers, and 46 (5%) had AT II blockers at the time of ICU admission.

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