Editorial

Mortality secondary to acute gastric variceal bleeding: a further prediction of outcome by acute kidney injury

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Bleeding from the rupture of esophageal varices is one of the most serious complications of portal hypertension. In fact, up to 20% of patients die acutely or within 6 weeks after the bleeding episode (1). Advanced Child-Pugh class, an elevated hepatic venous pressure gradient (HVPG, ≥20 mmHg), high model for end-stage liver disease (MELD) score values are the main predictors of this poor outcome (2-4). Therefore, many studies evaluated how to prevent variceal bleeding (or rebleeding) in cirrhosis. The body of numerous investigations demonstrated that esophageal bleeding occurs when the HVPG is equal or greater than 12 mmHg and the prophylactic administration of beta-blockers such as propranolol or carvedilol reduce the incidence of this poor outcome in patients with high-risk esophageal varices (5). More recently, in a selected group of patients, it has been demonstrated that trans-jugular intrahepatic porto-systemic shunt (TIPS) allocated during the first 3 days from the index bleed significantly reduces early-rebleeding and bleeding related mortality (the so called early-TIPS strategy of treatment) (6). Unfortunately, varices from portal hypertension are sometimes ectopic, being located in any part of the gut or in the stomach. In such last cases varices could bleed also in patients with a HVPG lower than 12 mmHg, the acute bleeding could not be predictable and could be frequently associated with chronic anemia (7). Endoscopic treatment of these gastric varices is hard due to their anatomy and the use of cyanoacrylate to eradicate them is neither always feasible, neither totally safe. Additionally, we do not know strong predictors of acute bleeding from gastric varices neither of the final outcome of this critical situation. Accordingly, few controlled trials have addressed the prevention and the acute management of these hemorrhages by including little series of patients thus limiting the possibility of adequately stratifying patients depending on the type of gastric varices and/or the severity of cirrhosis. Therefore, the use of NSBBs even in this clinical setting is recommendation of experts but not evidenced based, because the consistency and reliability of results published on this topic is not as strong as for esophageal varices. Alternatively, cyanoacrylate and balloon occluded retrograde transvenous obliteration (BRTO) are potential tools in the management of these patients, but the insertion of TIPS remains often the most efficacious in reducing the rebleeding risk and the bleeding related mortality (8). Data specifically obtained on exclusively gastric variceal bleeds are rare. In their recent paper, Hsieh *et al.* report the results of a retrospective analysis on 113 patients with cirrhosis hospitalized for gastric variceal bleeding (9). In this group of patients, one or more episodes of renal failure were recorded in accordance with the criteria of acute kidney injury (AKI) . Such patients showed a highly mortality rate if positive for AKI criteria during hospitalization. The result is not totally new in the clinical setting of cirrhosis. In 2001 Cárdenas *et al.* published similar findings and additionally showed that cirrhosis, per se, is a risk factor for the development of acute renal failure during upper-gastro-intestinal bleeding by comparing cirrhotic patients *vs.* a cohort of non-cirrhotic patients

matched for age and the severity of hemorrhage (10). At best of our knowledge, that experience has never been reproduced, furthermore, during last years the management of variceal bleeding has been better defined, and no studies have specifically addressed the reproducibility of that data in the clinical setting of acute variceal bleeding from gastric varices. The study from Hsieh *et al.* in part fills this gap and gives rise to some reflection on the topic.

In the specific, two are the main comments evoked by this study. The first one is related to the retrospectivity of data collection. It is necessary that an independent validation set, better if proceeding by a prospective investigation, would confirm these results in such a specific clinical setting. The second one refers to the relation of AKI with the bleeding outcome: is it a cause effect-relation or a simple association? First, the design of the study does not allow concluding any cause-effect relation with the outcome. Indeed, the investigation did not consider any specific interventional strategy targeted to manage the acute renal failure, therefore it is not possible to conclude that the improvement of creatinine values during hospitalization reduces the bleeding-related mortality, as it would be expected for a cause-effect relation. Furthermore, it is likely that the majority of patients included received high doses of terlipressin as recommended (5,8). This is an interesting point since the vasoconstrictor activity on splanchnic blood vessels by terlipressin is efficacious to manage any bleeding due to portal hypertension as well as hepatorenal syndrome type-1 (HRS-1), that could be considered the most life-threatening form of AKI in cirrhosis. During the last years, some authors have suggested terlipressin also for AKI management regardless the condition fulfills or not HRS-1 criteria. Therefore, the observation by Hsieh *et al.* that AKI is associated with mortality due to the hemorrhage from gastric varices even though patients received terlipressin suggests that there is not a cause-effect relation for this association in the overall series. A potential explanation for this apparent paradox may be that terlipressin was administrated without albumin that, by contrary, is part of the treatment of AKI/HRS-1 due to its oncotic and non-oncotic properties (11). Unfortunately, the indiscriminate use of albumin (as well as any other volume expander) during acute bleeding cannot be recommended due to the risk of further increasing portal pressure as consequence of the splanchnic overflow and the hyperdynamic circulation (12). For all these observations, we consider more likely that AKI in the clinical setting of gastric variceal bleeding is a simple hallmark of a hemodynamic weakness that is consequence of excessive blood loss and/or the systemic hemodynamic changes required by any acute hemorrhage. In other word, patients with AKI and acute hemorrhage from gastric varices may be at higher risk of hypovolemic shock and this observation could be extended to any hemorrhage in cirrhosis. Such an interpretation deserves potential important consequences for physicians, among them, the possibility of using AKI criteria to guide volume repletion in this clinical setting, but adequately designed human studies are warranted to convert this theoretical interpretation into and evidenced based recommendation.

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