Research Article

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Severe acute kidney injury associated with non-steroidal anti-inflammatory drugs in cirrhosis: A case-control study

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Background & Aims: Non-steroidal anti-inflammatory drugs (NSAIDs) may cause impairment of kidney function in patients with cirrhosis. Investigational studies demonstrated reversibility of kidney dysfunction after drug withdrawal, but information based on clinical practice is lacking. The aim of the study was to investigate the characteristics and outcome of Acute Kidney Injury (AKI) developing in patients with cirrhosis treated with NSAIDs.

Methods: Prospective cohort study in a tertiary referral center of all patients with NSAIDs-associated AKI seen from 2002 to 2014. For comparison, three control groups of patients with hypovolemic-induced AKI, type-1 HRS and ATN, respectively, were also evaluated. Urinary excretion of neutrophil gelatinase-associated lipocalin (uNGAL) was measured in a subset of patients.

Results: Thirty patients with cirrhosis and NSAIDs-associated AKI were identified. In 19 patients (63%) AKI was transient and kidney function rapidly recovered (4 ± 3 days) after NSAIDs withdrawal. In the remaining 11 patients (37%) AKI was more severe and persisted during hospitalization despite drug withdrawal. Patients with persistent AKI had remarkably higher uNGAL levels compared with those of patients with transient AKI (953 ± 1,198 *vs.* 83 ± 79 μg/g of creatinine, respectively, $p = 0.008$). Moreover, seven of the 11 patients with persistent AKI (64%) died within three months compared with only one of the 19 (5%) patients with transient AKI ($p = 0.001$). Mortality of persistent AKI was similar in NSAIDs patients compared to control groups. The only independent predictive factor of three-month mortality was persistent AKI.

Conclusions: Patients with cirrhosis treated with NSAIDs may develop severe AKI which may be irreversible and associated with poor short-term outcome.

Keywords: Cirrhosis; Kidney failure; AKI; Biomarkers; NGAL; NSAIDs.
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Abbreviations: PGs, Prostaglandins; COX, cyclooxygenase; NSAIDs, Non-steroidal anti-inflammatory drugs; AKI, Acute Kidney Injury; NGAL, neutrophil gelatinase-associated lipocalin; PRA, plasma renin activity; AKIN, Acute Kidney Injury Network.

Introduction

Prostaglandins (PGs) play a key role in the maintenance of kidney function in cirrhosis. A number of studies have demonstrated that PGs, are very important in the regulation of renal blood flow, glomerular filtration rate, sodium and water excretion in patients with cirrhosis, particularly in those with ascites [1–3]. PGs derive from arachidonic acid present in cell membranes through two metabolic steps. Firstly, arachidonic acid is converted into prostaglandin H2 through the effect of the enzyme cyclooxygenase (COX). Prostaglandin H2 is then transformed into the different PGs by the action of specific enzymes. The key regulator of PGs synthesis is the enzyme COX. PGs are synthesized in a number of kidney structures, including glomeruli, arterial vessels, tubules and interstitial cells [4,5]. The important role of PGs in the regulation of kidney function in cirrhosis was unequivocally demonstrated in a number of investigational studies in patients with cirrhosis in whom PG synthesis was inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) that are selective inhibitors of COX. These studies showed that administration of NSAIDs caused a reduction of renal blood flow and glomerular filtration rate and impairment of sodium and solute-free water excretion [1,3,4,6–10]. In these reports, glomerular filtration rate returned to baseline values after withdrawal of NSAIDs, which suggests that the effects caused by PG inhibition are short-lived and theoretically reversible after drug suppression. However, available information on the reversibility of kidney impairment is exclusively based on studies performed under strict investigational conditions in which NSAIDs were given either in single doses or for very short period of time. To our knowledge, there is no information available on the evolution of impairment of kidney

function in patients with cirrhosis who receive NSAIDs in daily clinical practice for management of pain or inflammatory conditions. Therefore, it is not known whether the impairment of kidney function that these drugs may cause in cirrhosis is always reversible after drug withdrawal. Neither is known whether it may affect patient's outcome. The current investigation reports the results of a prospective cohort study aimed at assessing the characteristics and evolution of patients with cirrhosis who developed Acute Kidney Injury (AKI) associated with treatment with NSAIDs.

Patients and methods

Study population

The study includes 30 consecutive patients with cirrhosis and kidney failure associated with the administration of NSAIDs admitted to the Liver Unit of the Hospital Clínic of Barcelona from April 2002 to April 2014. These patients were identified from a prospective database of 780 patients with cirrhosis and kidney failure seen during this period. The evaluation of all cases included asking patients and/or relatives about the use of NSAIDs in the preceding days before hospitalization. All patients included in the study had received NSAIDs outside the hospital and the impairment of kidney function was diagnosed at hospital admission. Exclusion criteria were: (1) patients under chronic hemodialysis; (2) patient with previous liver and/or kidney transplantation; (3) patients with hepatocellular carcinoma outside the Milan criteria or any other advanced malignancy; and (4) lack of informed consent. At admission, a detailed medical history was recorded. Laboratory tests were measured at admission and at regular intervals during hospitalization. In addition, a urine sample was collected in 12 patients for measurement of neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of tubular function [11,12]. Moreover, in 11 patients plasma samples were collected for measurement of plasma renin activity (PRA) and plasma concentration of norepinephrine.

Impairment of kidney function was defined using the AKIN criteria [13]. Briefly, a patient was considered to have AKI associated with NSAIDs when there was an increase in serum creatinine of $\geqslant$0.3 mg/dl or $\geqslant$50% over the baseline that developed during treatment with NSAIDs. Because all patients of the current cohort had impairment of kidney function at the time of admission to hospital, the baseline serum creatinine used to define AKI was the most recent stable serum creatinine value available within the previous three months. All patients had recent laboratory values and the average time elapsed between the last available serum creatinine and the first value at admission was of 46 ± 34 days.

AKI was graded in stages one to three [13–15]. AKI was considered transient if serum creatinine returned to values not greater than 0.3 mg/dl above baseline during hospitalization. Otherwise, AKI was considered persistent.

AKI was managed with withdrawal of the NSAIDs together with standard therapeutic measures, which included correction of electrolyte and/or acid-base abnormalities, if any, and renal replacement therapy, if indicated. Indications for renal replacement therapy were hyperkalemia, metabolic acidosis, anuria, and/or circulatory overload that could not be corrected with standard measures. Complications of cirrhosis were managed according to international guidelines. All patients gave written informed consent and the study was approved by the Institutional Review Board.

To evaluate the severity of NSAIDs-associated AKI, the study population was compared to three control groups composed of contemporary patients with cirrhosis with three different aetiologies of AKI: (1) hypovolemia-induced AKI (n = 60); (2) type-1 hepatorenal syndrome (HRS) (n = 30); and (3) acute tubular necrosis (ATN) (n = 21). Diagnostic criteria of these conditions have been reported elsewhere [12]. Patients with hypovolemic-induced AKI were matched by age and severity of cirrhosis, as estimated by the Child-Pugh score. By contrast, it was not possible to match patients with HRS and ATN by disease severity because liver failure was much more severe in these two groups of patients than in those with NSAIDs-associated AKI. Therefore, patients with ARS and ATN were only matched by age with those of the study group.

Statistical analysis

Comparisons of variables between groups were made with standard statistical tests. Survival probability curves were calculated with the Kaplan-Meier method and compared with log-rank test. Multivariate Cox proportional hazards model was used to assess variables independently related to three-month survival. All statistical analyses were performed using SPSS 20.0 software. Results for continuous variables are expressed as mean ± standard deviation. The significance level for all statistical tests was set at 0.05 two-tailed.

Results

Characteristics of the population

Study group

The characteristics of the group of patients with NSAIDs-associated AKI are shown in Table 1. Patients had relatively advanced cirrhosis and had suffered from previous complications of the disease, particularly ascites, gastrointestinal bleeding, and hepatic encephalopathy (24, 15, and eight cases, respectively). NSAIDs had been prescribed for management of pain related either to bone fractures, low back pain, or miscellaneous conditions. The specific drugs received were metamizol in 11 patients, ibuprofen in nine, diclofenac in six, aspirin in three, and etoricoxib in one patient. The average number of days of treatment with NSAIDs was 9 ± 14 days (range: 1 to 30 days). In all cases there was a clear chronological relationship between treatment with NSAIDs and development of AKI. At admission to hospital, most patients had complications of cirrhosis: 24 patients had ascites, 11 hepatic encephalopathy, four bacterial infections, and two gastrointestinal bleeding.

In addition to NSAIDs, six of the 30 patients had associated conditions that could have contributed to AKI: four patients had bacterial infections and two patients, gastrointestinal bleeding. No patient had shock, diarrhea, vomiting or any other condition that could have led to development of AKI, including the administration of potentially nephrotoxic agents other than NSAIDs.

Control groups

Baseline characteristics of the three control groups at time of hospital admission are shown in Table 1. As expected, patients with HRS and ATN had more advanced liver disease compared to the other two groups. The characteristics of the study group were similar to those of the hypovolemia-induced AKI group, except for a significantly greater MELD score, which was due to higher serum creatinine levels.

Characteristics and outcome of acute kidney injury

Study group

At admission, patients from the study group had severe impairment of kidney function with average serum creatinine of 3.4 mg/dl and estimated GFR of only 24 ml/min. Most patients had advanced AKI: 17 had AKI stage 2 or 3 (eight and nine patients, respectively), while 13 patients had AKI stage 1. Five patients had progression of AKI: one patient progressed from stage one to stage two and four patients from stage three required hemodialysis. Nineteen of the 30 patients (63%) eventually showed recovery of kidney function during hospitalization (transient AKI), while the remaining 11 patients (37%) had persistent AKI. Fig. 1 shows the evolution of serum creatinine values in patients from the study group categorized in two subsets according to whether they had transient or persistent AKI. Kidney biopsy was performed in one patient with persistent AKI and showed histological signs of acute tubular necrosis. Out of the