The Beneficial Effect of Beta-Blockers in Patients With Cirrhosis, Portal Hypertension and Ascites

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ABSTRACT

Background: Patients with cirrhosis and portal hypertensive complications have reduced survival. As such, it has been suggested that nonselective beta-blocker therapy in patients with advanced ascites is harmful. The aim of this study was, therefore, to determine the risk of mortality in patients with cirrhosis and ascites taking nonselective beta-blocker therapy for the prevention of variceal hemorrhage.

Materials and Methods: This study was a retrospective analysis of 2,419 patients with cirrhosis and portal hypertension admitted to Parkland Memorial Hospital (a university-affiliated county teaching hospital) from 2003-2010. Patients were subdivided into those with varices only, ascites only and those with both varices and ascites. The primary outcome measure for this study was all-cause in-hospital mortality.

Results: Overall, 68 of 1,039 (6.5%) patients taking beta-blockers died during their hospitalization, while 223 of 1,380 (16.2%) patients not taking beta-blockers died ($P < 0.001$). Beta-blocker use was also assessed in specific cohorts; mortality was 21.1% in patients with severe ascites with varices who were not taking beta-blockers compared with 8.9% in patients who were taking beta-blockers ($P = 0.05$). Overall, fewer patients taking beta-blockers died compared with those not taking beta-blockers in patients with varices only (6.4% versus 12.1%) and those with ascites with or without varices (6.6% versus 18.1%) ($P < 0.001$).

Conclusions: Mortality was lower in patients with cirrhosis and portal hypertension taking nonselective beta-blockers than in those not taking beta-blockers. The use of nonselective beta-blockers provided a significant survival benefit in patients with all grades of ascites, including those with severe ascites.

Key Indexing Terms: Mortality; Varices; Propranolol; Nadolol; Nonselective. **[Am J Med Sci 2016;351(2):169–176.]**

INTRODUCTION

Nonselective beta-blockers have become the standard of care treatment for patients with cirrhosis, portal hypertension and esophageal varices to decrease the risk of an index or subsequent episode of gastrointestinal hemorrhage.[1-7] Indeed, it has been firmly established that the use of nonselective beta-blockers in cirrhosis is effective for both primary and secondary prophylaxis.

It is also known that patients with cirrhosis who experience a decompensation event (gastrointestinal bleeding, ascites, encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome [HRS] and hepatocellular cancer) have a poor outcome and reduced survival.[8-10] The risk of death in patients after variceal bleeding is in excess of 40% at 1 year.[2] Development of ascites also predicts a poor outcome, and approximately 50% of patients die within 2 years.[4]

The use of beta-blockers in patients with cirrhosis, portal hypertension, esophageal varices and ascites has become extremely controversial, and it has been suggested that their use is associated with a poor outcome.[10,11] However, this has not been the authors' clinical experience. Therefore, the authors hypothesized that beta-blockers are beneficial in patients with portal hypertension and ascites. The aim of the present study was to determine the risk of mortality for patients with cirrhosis and varying severity of ascites on nonselective beta-blocker therapy for any reason (ie, primary prevention, secondary prevention of variceal hemorrhage, cardiovascular disease, etc.). The study examined a large, diverse and well-characterized cohort of patients with cirrhosis and portal hypertension, esophageal varices and different stages of ascites, including those taking and those not taking nonselective beta-blockers.

MATERIALS AND METHODS

This retrospective cohort analysis focused on the use of beta-blockers in patients with portal hypertension with or without ascites or esophageal varices or both. Patients were included only if they had known portal hypertension (ie, including gastroesophageal varices or ascites) and cirrhosis (defined below). This study included all unique patient admissions to Parkland Memorial Hospital, a University of Texas Southwestern

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teaching hospital, from January 1, 2003-December 31, 2010. Data were captured via a Cirrhosis Healthcare Registry that collects data on patients with known cirrhosis. The authors collected approximately 300 unique variables for each patient at the time of presentation, including demographic, clinical and historical data, such as medical comorbidities, presence of ascites, edema, history of gastrointestinal bleeding, hepatic encephalopathy, as well as laboratory data including bilirubin, prothrombin time, international normalized ratio (INR), aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine, electrolytes and platelet count. Clinical and laboratory variables reported were recorded at the time of hospital admission. Outcomes were recorded through the course of index hospitalization. This study was approved by the University of Texas Southwestern Institutional Review Board and met all criteria for good clinical practice.

Definitions

Cirrhosis was defined based on clinical features, including a history consistent with chronic liver disease, as well as a documented complication of chronic liver disease (ie, ascites, varices and hepatic encephalopathy) or imaging consistent with cirrhosis or liver histology consistent with cirrhosis or both. The cause of cirrhosis was determined according to the following criteria[1]: hepatitis C cirrhosis was defined as cirrhosis in a person with hepatitis C virus (HCV) RNA,[2] hepatitis B cirrhosis was defined by the presence of cirrhosis in patients with hepatitis B surface Ag,[3] alcoholic cirrhosis was determined from the provider's note in the presence of a history of alcohol abuse or dependence and the absence of other potential causes of liver disease,[4] other causes of cirrhosis were determined using standard diagnostic criteria (serology, histology, etc.), and[5] patients without any known cause of primary liver disease were considered to have cryptogenic cirrhosis.

Ascites was defined based on International Ascites Club criteria of uncomplicated ascites.[12] According to this expert group, uncomplicated ascites is ascites that is not infected and not associated with the development of the HRS. Grade I (or mild ascites) is only detectable by ultrasound examination. Grade 2 (or moderate ascites) is manifested by moderate symmetrical distension of the abdomen. Grade 3 is large or gross ascites with marked abdominal distension. Because the labeling of ascites was not identified as diuretic-tolerant or intolerant or “refractory” in the cohort, an attempt was not made to further subcharacterize the groups.

Varices were confirmed by a documented endoscopic evaluation. Varices were identified in multiple ways including on routine screening endoscopy or during endoscopic evaluation for acute gastrointestinal bleeding; when varices were documented endoscopically, this was recorded as part of the patient's history. Not all patients underwent endoscopy during the hospital admission. The use (or nonuse) of nonselective beta-blockers was captured as a unique variable at the time

of admission. Use of nonselective beta-blockers (ie, propranolol, nadolol and carvedilol) at the time of admission, as determined by history and medicine reconciliation, was considered to be consistent with beta-blocker use (regardless of dosage or time of treatment). Of note, the presence or absence of varices was captured at the time nearest to the hospitalization period so that if patients had varices previously and had been eradicated (which occurs frequently), they would have been categorized as not having varices. Patients having had transjugular intrahepatic shunts were excluded.

Statistical Analysis

Given the large size of the cohort and the authors' desire to understand whether beta-blockers may have had an effect that was predicated on the amount or severity of ascites or both, the authors decided *a priori* to divide the cohort into groups based on the presence or absence, and severity, of ascites. The primary outcome measure was all-cause hospital mortality. Demographics, as well as clinical and laboratory characteristics were summarized using means or proportions as appropriate. Comparisons between groups used analysis of variance for quantitative values and chi-square for qualitative measures. Comparisons in mortality rates between those patients on and not on beta-blockers were determined using the Fisher's exact test for differences in proportions. The 95% CIs for the mortality rate were computed using exact binomial distribution. To identify which clinical and laboratory markers predict an increase in risk of mortality in patients, they performed logistic regression analyses. Univariate logistic regression analysis was performed to examine the risk of mortality based on liver disease-related markers, including total bilirubin, iINR, serum creatinine, aspartate aminotransferase, alanine aminotransferase, complete blood count, as well as model for end-stage liver disease (MELD) score, Child-Turcotte-Pugh score and Child-Pugh class. The use (or nonuse) of nonselective beta-blockers was also included in the analysis as a predictor of mortality. A multivariable logistic regression analysis was used to develop a predictive model for mortality. Potential predictive variables were selected using a hierarchical selection approach that included univariate and multivariable stepwise selection to develop an optimal statistical model. In the text, the term “model” refers to this predictive logistic equation. The final multivariable model was selected based on the Akaike information criterion to identify risk factors that independently predict mortality. An additional diagnostic for the logistic model was a Receiver Operation Characteristic (ROC) curve analysis that is used to estimate how well a multivariable logistic model fits the observed data.[13] Similar in interpretation to correlation coefficients,

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