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Role of Non-Selective Beta Blockers in Hepatocellular Carcinoma: An Analysis in Patients with Cirrhosis and Portal Hypertension

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There are many different biochemical processes responsible for the hepatocellular carcinoma (HCC) development that can be targeted for the prevention or halt progression of the HCC. Non-selective beta-blockers (NSBB) affects a multitude of intracellular biochemical and signaling pathways involved in carcinogenesis. Aim: To determine if NSBB may be protective for HCC in patients with cirrhosis and portal hypertension. Methods: We retrospectively enrolled 200 patients from medical records diagnosed with cirrhosis and portal hypertension between January 2001 and December 2013. Eighteen patients were excluded (taking selective beta-blocker and/or unavailable medical records). The etiology of cirrhosis, use of NSBB, demographics and the presence of HCC was collected. Result: There were 140 males and 42 females. The mean age for portal hypertension with cirrhosis without HCC was 53.5 ± 11.4 & with HCC was 62.2 ± 9.5 years. Univariate analysis of the association of NSBB with HCC yielded OR = 0.11 (95% CI: 0.04 to 0.25); $p < 0.0001$, suggesting a protective effect of NSBB. Multivariable analysis suggests virtually no change when the Odds ratio (OR) was adjusted for diabetes mellitus (DM), alcohol use, Hepatitis B virus (HBV) status, Black race and age ≥ 53 . There was a slight increase in the OR adjusted for statin use. Conclusion: This study highlights association of NSBB use in the patients with liver cirrhosis and portal hypertension for prevention of HCC.

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Key Words: Cirrhosis, portal hypertension, liver cancer/hepatocellular carcinoma, non-selective B blockers

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and seventh most common cancer in women.¹ According to American Cancer Society, about 30,000 new cases are diagnosed each year. Major risk factors for development of HCC include hepatitis C virus infection (HCV), hepatitis B virus infection (HBV), alcoholic liver disease and nonalcoholic fatty liver disease (NAFLD), but virtually cirrhosis of almost any cause is the risk factor. Age-adjusted incidence of the HCC has been going up in recent decades. The incidence has almost doubled in the past two decades and it is expected to continue to rise as a consequence of high hepatitis C infection rates between 1960 and 1990.²

There are many biochemical processes responsible for the

HCC development that can be targeted for the prevention or halt progression of the HCC. Various biochemical processes include (1) increased level of reactive oxygen species (ROS) mediated lipid peroxides, which participate in chain reactions that amplify damage to bio molecules, including DNA and at the end result of DNA attack gives rise to the mutations that may involve tumor suppressor genes or oncogenes, and cause cancer.³ (2) Mitochondria are crucial for cellular energy production, cell survival and major regulator in the intrinsic apoptotic pathway so mitochondrial dysfunction by certain gene mutations in mitochondria may lead to cause apoptotic resistance, evolves into hepatocarcinogenesis and promote HCC progression.⁴ (3) HCV proteins trigger ROS generation through induction of NADPH oxidase 4 expressions and autocrine TGF β -dependent mechanism. The ROS then activates mitogen-activated proteins, extracellular signal-regulated kinases, or angiogenesis along with induction of DNA damage.⁵ (4) Vascular endothelial growth factor (VEGF) is associated with the development of liver tumor neovascularization and basic fibroblast growth factor (FGF) is involved in infiltration of cancer cells into the tumor

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capsule in HCC.⁶ (5) Linear relation exists between level of catecholamines and severity of liver disease. More advanced disease is associated with higher levels of catecholamines.⁷ (6) Bacterial translocation, across the edematous bowel wall, represents a large inflammatory load to the cirrhotic liver. It exposes hepatocytes to chronic inflammation, thus contributing to carcinogenesis.⁸

Non-selective beta-blockers (NSBB) affects a multitude of above mentioned intracellular biochemical and signaling pathways involved in carcinogenesis. These include (1) preventing lipid peroxidation of the membranes, (2) attenuating mitochondrial dysfunction, (3) inhibiting Bax-mediated cytochrome C release, NADPH oxidase and protein kinase C activity, (4) decreasing vascular endothelial growth

factor (VEGF) / basic fibroblast growth factor gene expression. (5) antagonizing catecholamine driven cell migration, tumor angiogenesis, invasiveness and proliferation (6) decreasing bacterial translocation and reducing the partial load of pro inflammatory bacterial products. (7) preventing or reducing cancer progression, by inhibiting cAMP-responsive element-binding protein (CREB), NF- κ B, and activator protein (AP-1), inducing apoptosis, or reducing matrix metalloproteinase (MMP)-9 activation and tumor angiogenesis.⁹⁻¹⁶

Because NSBB are regularly used as prophylaxis for portal hypertension in cirrhotic liver disease, the purpose of this study was to look for a possible association of NSBB with HCC.

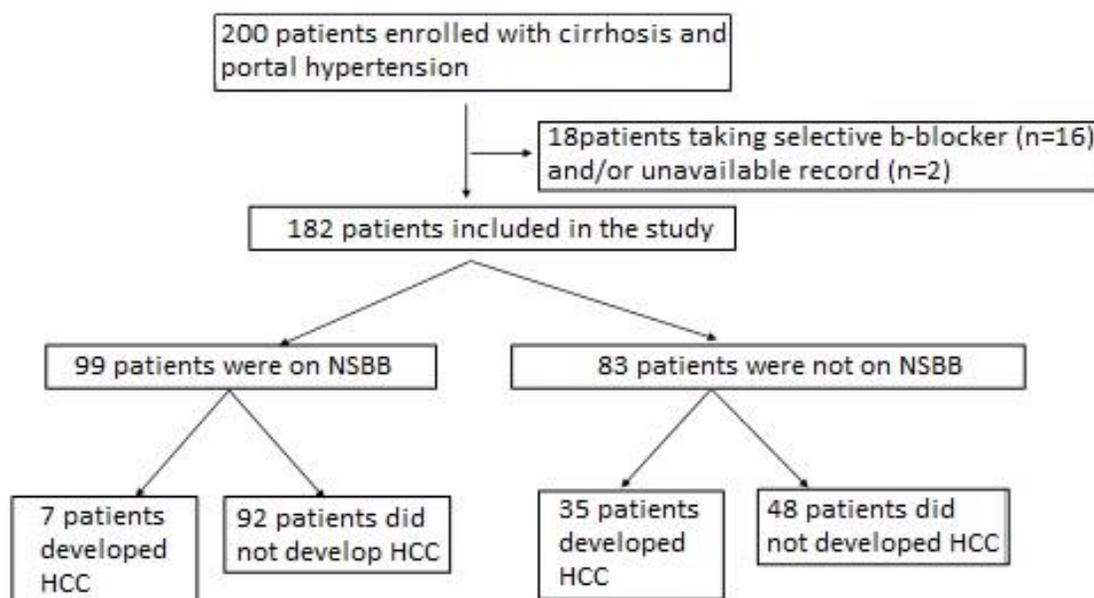


Figure 1. Flow chart of the protocol.

METHODS

Protocol, patients and setting

This is a retrospective analysis of 200 consecutive patients, age ≥ 18 years, from Jan 2001 to 31 Dec 2013, with a diagnosis of portal hypertension and cirrhosis, with or without HCC. The institution at which the study was conducted is a 700-bed tertiary-care teaching hospital in northeastern USA. Excluded from the original cohort were 16 patients taking a selective β blocker and 2 patients for whom insufficient data were available. The flow chart of the study is shown in **Figure 1**.

The study was given exempt status by the Institutional Review Board of St. Joseph's Healthcare System, which operates the center where the study was conducted.

Statistical analyses

For this study, α was set at 0.05; thus values of $p < 0.05$ were required for statistical significance. Potential confounders were considered as covariates if baseline differences between the groups had a p -value $\leq 5\alpha$, i.e., $p \leq 0.25$. The continuous variable (age) was found to be not significantly different from a normal distribution by the D'agostino-Pearson omnibus normality test. Therefore age is expressed as mean ± 1 . Standard deviation (SD) and between-group age differences evaluated by the t-test. The cutoff for dichotomizing age for the two groups was determined by receiver operating characteristic (ROC) curve analysis.

For categorical variables, univariate association was evaluated by cross-tabulating exposures with the outcome

and tested for statistical significance with Fisher's exact test for 2 x 2 contingency tables and with chi-square for tables with larger numbers of cells (race/ethnicity). Because of the retrospective nature of the study, the odds ratio (OR) and 95% confidence interval (95% CI) was used as a measure of effect size. Multivariable association, using covariates as described, above, was assessed by binary logistic regression.

Analyses were conducted using the Prism® software (GraphPad Corp., San Diego, CA, USA) and SPSS® v. 21 (IBM Corp., Armonk, NY, USA).

Table 1. Baseline Demographics.

Characteristics	HCC Present (42)	HCC Absent (140)	p- value
Age (Mean±SD)	62.2 ±9.5	53.5 ±11.4	< 0.0001
Gender (F/M)	7/35	35/105	0.303
Race/Ethnicity			0.242
Black vs all others	12	21	0.066
Hispanic vs all others	19	77	0.291
White vs all others	8	33	0.675
Others vs all others	3	9	
DM (+/-)	9/33	47/93	0.182
HCV (+/-)	21/21	57/83	0.283
HBV (+/-)	8/34	13/127	0.099
Ethanol use (+/-)	16/26	77/63	0.078
Statin use (+/-)	5/37	4/136	0.032

RESULTS

Baseline Characteristics of the Subjects

Table 1 gives the demographic and clinical characteristics of the two groups. There were 140 males and 42 females. The mean age for portal hypertension with cirrhosis without HCC was 53.5 ± 11.4 & HCC was 62.2 ± 9.5 years. The distribution of race was 96 (52.7%) Hispanic & 41 (22.5%) Caucasian. Causes of cirrhosis were alcohol 93 (51%), followed by HCV 78 (42.8%). Ninety-nine (Propranolol = 97, Nadolol = 2) patients were on NSBB. Forty-two patients (M = 35, F = 7) had a diagnosis of HCC. Among those examined, age, race/ethnicity, diabetes, presence of HBV, ethanol and statin use demonstrated p-values ≤ 0.25 and were included in the multivariable model. Race/ethnicity data were further dichotomized post hoc. This analysis yielded black race (p = 0.066) as a covariate.

Association of NSBB with HCC

Analysis of the association of NSBB with HCC on a univariate base yielded OR = 0.11 (95% CI: 0.04 to 0.25); p < 0.0001, suggesting a protective effect of NSBB. In males, the odds were lower in NSBB [OR 0.112, CI 95% (0.042, 0.295) p < 0.0001]. Significantly lower odds were also found in HCV [OR 0.17, CI 95% (0.056, 0.513) p < 0.0001], alcohol [OR 0.039, CI 95% (0.005, 0.309) p < 0.0001], Hispanic [OR 0.146, CI 95% (0.044, 0.479) p = 0.0008] and black race [OR 0.062, CI 95% (0.01, 0.386) p = 0.001]. Statistical significance was not reached in females [OR 0.174, p = 0.051], HBV subgroup [p = 1] and Caucasian subgroup [p = 0.2]. Multivariable analysis suggests virtually no change in the OR and 95% CI when age [at a cutoff of 53 years] (OR: 0.11, CI: 0.04 to 0.28), black race (OR: 0.1, CI: 0.04 to 0.24), HBV status (OR: 0.11, CI: 0.04 to 0.26), ethanol use (OR:

0.1, CI: 0.04 to 0.24) and diabetes mellitus (OR: 0.1, CI: 0.04 to 0.25) were included as covariates. Interestingly, statins slightly mitigated the protective effect of NSBB, the OR, adjusted for statins, was 0.12 (95% CI: 0.05 to 0.29). (**Figure 2**)

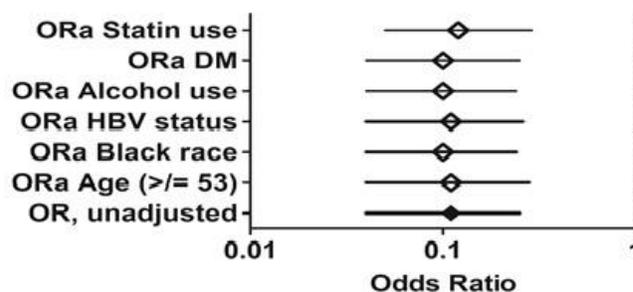


Figure 2. Forest plot comparing univariate OR and 95% confidence interval (CI) with those adjusted for covariates.

DISCUSSION

In our study, we assessed the association of NSBB in the HCC prevention in patients with cirrhosis and portal hypertension. We found that NSBB treatment is associated with lower incidence of the HCC in patients with cirrhosis and portal HTN.

As the incidence of HCC is increasing, it is important for us to look for preventive measures to stop the growing burden and health care cost of HCC.² Use of HBV vaccination dramatically reduced the prevalence of HBV infection and there has been a concomitant decrease in the incidence of hepatocellular carcinoma.¹⁷ The literature suggests the use of antiviral therapy to control HBV and HCV infection and achieving sustained viral response substantially reduces but does not eliminate the risk of HCC.¹⁸⁻²⁰ Statin use also has been associated with a lower risk of HCC in patients with HBV and HCV infection.²¹⁻²² One common limitation exists with all above-mentioned preventive interventions; that is, once cirrhosis is established the effectiveness of these interventions to prevent HCC development and progression is questionable.^{18,20-23} While, NSBB is the only intervention which might work in the patients with advanced cirrhosis to prevent HCC.⁵

To our knowledge, two retrospective studies have been done so far to evaluate the protective effect of NSBB in the patients with cirrhosis. Nkontchou et al retrospectively reviewed 291 patients with compensated hepatitis C virus related cirrhosis showed NSBB use decreased HCC incidence.⁵ Kim et al reviewed 273 patients with all cause cirrhosis and it did not show any relation between NSBB and HCC incidence.²⁴ There are many other benefits of NSBB reported in the literature for cirrhotic patients and some tumors. NSBB has been shown to decrease mortality in patients with cirrhosis via reducing the rate of gastrointestinal

bleeding and decreasing incidence of spontaneous bacterial peritonitis.^{25,26} In ovarian and breast cancer NSBB has shown promising results in tumor prevention and growth.^{27,28} The anti-angiogenic effects of NSBB in hemangiomas are well documented.²⁹

It is clear from our study that individuals who were not on the NSBB were more likely to develop HCC. NSBB is easily available, affordable and are also well tolerated by most of the patients. So this strategy may decrease incidence of HCC in patients with cirrhosis.

Major limitation of our study are unknown compliance and duration of NSBB therapy, duration from onset of portal HTN to development of HCC, and data regarding antiviral therapy. Short follow up period which is 3 years.

CONCLUSION

This study highlights association of NSBB use in patients with liver cirrhosis and portal hypertension for prevention of HCC. It is also clear that further studies, especially randomized control trial need to be carried out to evaluate the importance of NSBB in HCC prevention. If favorable effects of NSBB will be confirmed in such a trial, this would be significant since the majority of cirrhotic patients would need beta blockers and they are at the high risk for HCC.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

ETHICAL APPROVAL

This work meets all the ethical guidelines.

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