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Non-Selective Beta Blocker Therapy Improves Survival in Patients Receiving Alfapump©

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Abstract

Background: Ascites is the common cause of decompensation in patients with cirrhosis. It has been ascertained that 5% to 10% of patients with end stage liver disease showed in case of compensation the develop of ascites every year. The alfapump© reduces the need for large volume paracentesis and can improve life quality. The aim of our study was to assess the role of the use of Non-Selective Beta-Blocker (NSBB) characteristics and outcomes of patients with cirrhosis receiving alfapump© and to find predictors of a longer life in a palliative concept.

Methods: Seventeen (13 males) patients with liver cirrhosis receiving an alfapump© were included in this case-series. Clinical parameters were assessed before the insertion of the alfapump© and during follow-up. As part of the follow-up, all patients received the standard of care as recommended by European Association for the Study of the Liver and DGVS.

Results: Could generally be identified as the cause of death. If the patients were stratified according to the use of a non-selective beta-blocker, we can see that the group taking non-selective beta blocker had a longer survival. These data to verify previous finding that NSBB in this very high-risk patient may delay infections and improve outcome.

Conclusion: This study suggests a protective effect of NSBB in patients after implantation of an alfapump©. Although confirmation is needed, this may help management of patients receiving the device.

Keywords: Liver; Cirrhosis; Ascites; Alfapump©; Non-selective beta blocker

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Introduction

Portal hypertension develops usually during the progression of chronic liver disease and leads to various complications, such as variceal hemorrhage, ascites and hepatorenal syndrome. The Baveno-consensus-conferences over the decades have elaborated on the step-wise prevention and treatment of varices, having especially Non-Selective Beta Blockers (NSBB) and endoscopic band ligations the mainstay of the strategy [1-3]. While over time the numbers of admissions for variceal bleeding have decreased, the most common manifestation of decompensation in cirrhotic patients is ascites, which has increased over time [4].

However, every year [1], 5% to 10% of patients with compensated advanced chronic liver disease develop ascites, which is also associated with a poor prognosis. The two-year mortality rate for this group of patients is 40% to 50% [5]. The insertion of Transjugular Intrahepatic Portosystemic Shunt (TIPS) reduces portal hypertension and consequently ascites development [6]. However, there is a group of patients with ascites who may have contraindication for TIPS, such as very advanced liver failure, episodes of recurrent overt hepatic encephalopathy without identifiable trigger, heart failure and pulmonary arterial hypertension. Besides TIPS implantation, alternative are repetitive large-volume paracentesis with albumin infusion [7,8], indwelling peritoneal catheters [9], liver transplantation and automated low-flow ascites peritoneal-vesical pump [10-12] (alfapump© VR, Sequana Medical, Belgium).

Patients with refractory ascites, not suitable for TIPS insertion due to contraindications, were evaluated for the implantation of an alfapump©. The alfapump© reduces the need for large volume paracentesis and can improve the quality of life in selected patients [13]. But due to its symptomatic

Table 1: Patient characteristic.

General Parameters	All	NSBB	No NSBB	P
Gender (male/female)	13/4	8/2	5/2	n.s
Age	65 (47/81)	65 (47-79)	65 (49-81)	n.s
Etiology (alcohol / other)	7-Oct	5-May	2-May	n.s
Child category (A/B/C)	(0/14/3)	(0/8/2)	0/6/1	n.s
MELD score	13 (6-26)	12/8/2022	13 (6-26)	n.s
varices (present/absent)	(11/6)	10/0	1/6	0.03
Hepatic encephalopathy (present/absent)	(12/5)	7/3	5/2	n.s
Spontaneous bacterial peritonitis before alfapump©	0	0	0	
DM (present/absent)	(5/12)	3/7	2/5	n.s
COPD (present/absent)	(1/16)	1/9	0/7	n.s
Cause of death (infections / others)	(17/0)	(17/0)	(17/0)	
Laboratory Values				
Sodium (mmol/L)	136 (120-146)	134 (120-146)	136.8 (126-144)	n.s
Potassium (mmol/L)	4.1 (3-6)	4.3 (3-6.0)	3.9 (3.4-4.5)	n.s
Creatinine (mg/dL)	1.5 (0,5-3.9)	1.45 (0.6-2.8)	1.5 (0.5-3.9)	n.s
Urea (mg/dL)	62 (22- 126)	65 (22-126)	59.4 (36-122)	n.s
Bilirubin (mg/dL)	1.7 (0.3-4.7)	1.6 (0.8-2.8)	1.6 (0.3-4.7)	n.s
Gamma-glutamyl transferase (U/L)	186 (23-951)	202 (23-543)	173 (43-951)	n.s
alanine aminotransferase (U/L)	28 (6-59)	32.7 (17-56)	23.9 (6-59)	n.s
Aspartate aminotransferase (U/L)	42 (17-78)	49.7 (37-78)	36.7 (17-59)	0,036
Albumin (g/L)	31.7 (23-39.6)	33 (28-39)	30.8 (23-39.6)	n.s
International normalized ratio	1.3 (1-2.1)	1.3 (1-1.9)	1.3 (1-2.1)	n.s
Hb (g/dL)	9.7 (8-14)	9.3 (7-22.9)	10.4 (7-14)	n.s
Medical Therapy				
Non-selective beta blocker (yes/no)	(10/7)	10	0	
Rifaximin (yes/no)	(9/8)	(5/5)	(4/3)	

nature, does not affect portal hypertension [14]. NSBB, which are controversially discussed in ascites, indeed have been shown to improve overall survival and prevent ascites development and ascites in compensated and decompensated patients [5,15]. Therefore, the aim of our study was to evaluate the role of NSBB in patients receiving an alfapump©.

Patients and Methods

Brief description of the procedure

The alfapump© system is an approved medical product. It consists of three implantable components.

- A subcutaneous pump including a battery that is recharged by induction
- A catheter that suggests the ascites from the peritoneal cavity into the pump
- A catheter as a connection from the pump to the bladder

The alfapump© is implanted using minimally invasive surgical techniques as previously described in detail by Stirnimann et al. [8].

Patients and data collection

In this retrospective study, we enrolled 17 consecutive patients suffering from liver cirrhosis who were admitted to the Department of Internal Medicine I, University Clinic Bonn, Bonn, Germany, to evaluate the option of a receiving an alfapump© between 2013 and 2016.

The endpoint of the study was defined as dead (n=17). Clinical data of all patients were collected by trained medical personnel during hospital visits and included general clinical data, medical history, medication and laboratory parameters.

Initially, all patients received a standardized evaluation for TIPS insertion. If patients meet exclusion criteria for TIPS, the further evaluation to the alfapump© system was made. The focus beside the operability of the patient was to exclude those with previous spontaneous bacterial peritonitis and current infections. Furthermore, the clinical assessment that the patient has a survival probability of less than 6 months was defined as exclusion criteria. Follow-up care was preceded in accordance with the current European Association for the Study of the Liver guidelines for the management of patients with liver cirrhosis. Patients gave their written consent for the collection of their data. The study was approved by the ethical committee of the University of Bonn in line with the Declaration of Helsinki (No. 121/14).

Statistical analysis

The data were collected retrospectively and evaluated by means of

SPSS statistical analysis software (IBM SPSS Statistics for Windows, Version 22.0, released 2013. Armonk, NY: IBM Corp.). P-values <0.05 were statistically significant.

Unless otherwise declared, data were presented as means ± standard deviation or standard error of the mean and ranges. To compare the survival rates of patients by using the log-rank test, Kaplan-Meier plots were used. Multivariate Cox regression analysis (forward stepwise likelihood quotient) using the significant predictors in the univariate analysis was performed to identify independent predictors of survival. For the selection of cut-off values, Receiver Operating Characteristics (ROC) analysis with survival as endpoint was calculated.

Results

General characteristics of patients at baseline

The clinical characteristics at baseline before an alfapump© implantation are presented in Table 1. A total of 13 male and 4 female patients with a mean age of 65 years suffering from liver cirrhosis were included (Table 1). The main etiology of cirrhosis was alcohol-related (10 patients). In most cases TIPS placement was not possible due to hepatic encephalopathy (12 patients). Most of these patients were presented with Child B (14 patients), and 3 patients presented with Child C (Table 1). Median MELD-score (Model for End-Stage Liver Disease) was 13. Varices were present in 11 patients without a history of a bleeding episode. No Patients with history of spontaneous bacterial peritonitis received an alfapump©.

The cause of death in all patients was an infection with consecutive liver failure. Drug therapies for patients were also recorded. Ten patients received non-selective beta blocker therapy as treatment of esophageal varices; 9 patients received therapy with rifaximin due to hepatic encephalopathy.

Comparisons between the patients receiving or not NSBB

Interestingly, the comparison of the groups shows no significant differences in the groups except for the presence of varices and aspartate aminotransferase. However, this distribution was to be expected, since the stratification characteristic of taking NSBB corresponds to the treatment of these esophageal varices.

Survival Analyses

Infections were the main trigger for decompensation leading to ACLF and death. If the patients were stratified according to the use of a beta blocker, it was found that the group treated with non-selective beta blockers had a longer survival. In univariate time-to-event analysis, lower creatinine and use of a beta blockers were identified to be associated with overall survival (Table 2). In multivariable Cox regression analysis, these parameters are confirmed (Table 2).

Discussion

This study describes that NSBB may be associated with improved outcome in patients after implantation of an alfapump©. The role of the beta-blocker in the therapy of cirrhosis and in particular portal hypertension is long and subject to debates. Therefore, new insights into the effects of beta-blockers are the aim in ongoing studies.

Propranolol was first described to decrease portal pressure in the 1980-ies, and showed to be very effective in the prevention of variceal bleeding [16]. The physiological effect of beta blockers is based on the increase resistance to portal blood inflow at the hepatic circulation. Interestingly, NSBB may also protect against spontaneous bacterial peritonitis and decompensation in cirrhotic patients [15,17-23]. However, reports describe deleterious effect of NSBB in patients with refractory ascites [24], especially if SBP develops [14]. These controversial discussions led to the idea of the therapeutic window, which recommended the administration of beta blockers in the early phase of cirrhosis [25].

In our collective, infections were the trigger for the decompensation with a fast development of sepsis and ACLF. However, the type of infection in patients with implant, are not always clear, since spontaneous bacterial peritonitis cannot be differentiated from secondary bacterial peritonitis.

All our patients have severe portal hypertension and all of them develop ACLF, so per definition are pre-ACLF-patients [26]. The main cause of death in our cohort was development of ACLF triggered by infections, as known to be the most frequent precipitant [27]. It is known that patients with renal failure and circulatory dysfunction develop acute-on-chronic liver failure due to the elevated inflammatory status [28,29]. A sub-analysis of the CANONIC trial showed, that non-selective beta blocker administration improved 28-day survival in patients with acute-on-chronic liver failure [22]. Potential mechanisms could be increased gut motility and reduced bacterial translocation known to be caused by beta-blockade, which in turn may decrease systemic inflammation. Previous studies assume this effect of non-selective beta blockers may represent by a direct drug effect, even in severe septic shock [30].

Furthermore, Tergast et al. [31] reported better survival in 254 patients with acute-on-chronic liver failure under non-selective beta blockers. Non-selective beta blocker use remained a positive prognostic factor after adjusting for potential confounders in a multivariate model, while early interruption of non-selective beta blockers was associated with lower 28-day transplant-free survival [31]. These data may support our finding that NSBB in these very high-risk patients may delay infections and improve outcome.

This study has many limitations such as its retrospective character, small cohort and the selection bias. Still these data suggest a potential useful strategy to decrease portal hypertension in patients with a symptomatic treatment of ascites.

Conclusion

In patients receiving alpha pump implantation, NSBB may be beneficial, although this study requires validation.

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Authors Contribution

C.J.: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis of data; critical revision of the manuscript for important intellectual content. R.W: Acquisition of data; drafting of the manuscript; statistical analysis of data; critical revision of the manuscript for important intellectual content. M.P, J.C, N.B, D.K, A.H & J.L.: Acquisition of data; analysis and interpretation of data; drafting of the manuscript. C.S.: Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; J.T.: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript;

Table 2: Univariate time-to-event analysis of collected data and multivariable cox regression analysis (Forward Stepwise Likelihood Quotient) using the variable from univariate analysis to predict outcome.

Parameters	Univariate Analysis				Multivariate Analysis			
General Parameters	P	Hazard ratio	Confidence interval 95%		P	Hazard ratio	Confidence interval 95%	
			Lower	Upper			Lower	Upper
Gender	n.s.	0.914	0.289	2.888				
Age	n.s.	1.019	0.966	1.074				
Etiology	n.s.	1.366	0.475	3.933				
Child category	n.s.	0.944	0.263	3.394				
MELD score	n.s.	1.074	0.982	1.174				
varices	n.s.	1.748	0.617	4.958				
Hepatic encephalopathy	n.s.	0.649	0.201	2.099				
DM	n.s.	0.617	0.206	1.85				
COPD	n.s.	0.553	0.068	4.511				
Transthoracic echocardiography Parameters								
Mitral insufficiency	n.s.	3.384	0.813	14.085				
Aortic insufficiency	n.s.	0.836	0.266	2.630				
Aortic stenosis	n.s.	0.39	0.043	3.498				
Tricuspid insufficiency	n.s.	2.312	0.257	20.755				
Ejection fraction	n.s.	0.983	0.933	1.034				
Laboratory Values								
Sodium	n.s.	0.916	0.83	1.012				
Potassium	n.s.	1.211	0.41	3.572				
Creatinine	0.017	2.835	1.209	6.648	0.021	3.049	1.184	7.854
Urea	n.s.	1.008	0.99	1.026				
Bilirubin	n.s.	1.082	0.717	1.633				
Gamma-glutamyl transferase	n.s.	1	0.998	1.002				
alanine aminotransferase	n.s.	0.995	0.965	1.026				
Aspartate aminotransferase	n.s.	1.015	0.983	1.047				
Albumin	n.s.	1.005	0.917	1.102				
International normalized ratio	n.s.	1.811	0.369	8.899				
Hemoglobin	n.s.	0.768	0.572	1.030				
White blood cell	n.s.	0.876	0.732	1.049				
C-reactive protein	n.s.	0.924	0.846	1.009				
Medical Therapy								
Beta Blocker	0.006	0.104	0.02	0.53	0.007	0.099	0.018	0.530
Rifaximin	n.s.	0.934	0.336	2.597				

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