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Non-selective beta-blockers in cirrhotic patients with refractory ascites: where are we?

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HIGHLIGHTS

- The use of NSBB in cirrhotic patients with refractory ascites is questioned due to divergent evidence between studies.
- This article aims to gather current evidence on the use of NSBB in this subgroup of patients, evaluating their outcomes.
- Clinical judgment, together with hemodynamic parameters, remains the main definers of the maintenance of these medications.

ABSTRACT – Background – The established use of non-selective beta-blockers (NSBB) in the primary and secondary prevention of esophageal varices has recently been questioned in the subgroup of patients with diuretic-refractory ascites. **Objective –** Critically analyze the body of evidence on the topic in order to assist clinical decisions. **Methods –** A literature review was carried out in the Pubmed® and Scielo® databases. In total, 20 articles between 2010 and 2023 were read by independent researchers. **Conclusion –** It remains doubtful whether the use of NSBB is deleterious in cirrhotic patients with refractory ascites, however our literature review allows us to conclude that these drugs should not be proscribed in these patients. On the contrary, a doctor-patient decision based on tolerability and hemodynamic parameters certainly seems to be a safe conduct.

Keywords – Non-selective beta-blockers; refractory ascites; mortality.

INTRODUCTION

Liver cirrhosis has as one of its main complications esophageal varices, which historically play an important role in the mortality of these patients. The use of non-selective beta-blockers (NSBB) in cirrhotic patients to prevent decompensation is well endorsed in the literature, with high-impact studies demonstrating their effectiveness beyond the primary and secondary prevention of variceal bleeding. Over the years, it was proven that reducing portal pressure had other benefits that were already naturally expected, taking into account the pathophysiology of cirrhosis: compensated cirrhotic patients using beta-blockers not only developed less ascites than those who were being treated with placebo[1], but also had fewer spontaneous bacterial peritonitis (SBPs)[2]. Therefore, it was no surprise when Turco et al. published a meta-analysis in which the odds ratio of death and

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liver transplantation was 53% lower in cirrhotic patients responding to beta-blockers, that is, in those in whom there was actually a reduction in the pressure gradient venous[3], regardless of the presence of ascites. Furthermore, these drugs were found to have additional roles in reducing systemic inflammation (interpreted based on leukocyte and C-reactive protein levels)[4].

However, in 2010, an observational study published by Sersté and his collaborators brought to light a doubt that hovered among doctors: whether beta-blockers would, in fact, be safe in patients with refractory ascites. The findings of this study raised the hypothesis that the use of NSBB would not be beneficial in patients with advanced stages of liver cirrhosis. A possible pathophysiological mechanism that would explain such a correlation would be the fact that NSBB would reduce cardiac reserve and thus impair the fine compensatory hemodynamic mechanisms present in cirrhotic patients, especially the sympathetic nervous system, responsible for maintaining tissue oxygenation and renal perfusion.

Subsequent studies were unable to demonstrate, with high reliability, whether Sersté's findings were reproducible. However, several articles have postulated that caution regarding this group of patients with such an unfavorable prognosis and, therefore, high mortality, should be the norm. Thus, the "window hypothesis" was supported, which, in short, supported that there would be a limit when the risks would outweigh the benefits of these drugs. In fact, the Baveno consensus encourages this hypothesis, after all it recommends that hemodynamic parameters such as systolic blood pressure, natremia and evidence of acute kidney injury are the limiting factors in the group of patients with refractory ascites.

We understand that the pathophysiology of decompensated cirrhotic patients, that is, their poor distribution (evidenced by peripheral arterial vasodilation) speaks against the use of these medications, but we also recognize that the benefits of NSBB go beyond reducing portal pressure. Therefore, our study set out to study in depth the few articles previously published on the topic. We need to know when is the ideal time to withdraw such medications from our patients, otherwise we risk committing iatrogenic injuries.

METHODS

When preparing this study, a database search was carried out on the topic: use of beta-blockers in patients with refractory ascites. To this end, the descriptors used in the Pubmed® and Scielo® databases were "cirrhosis", "ascites" and "beta-blockers". Only articles in the English language were selected. Furthermore, the analysis remained restricted to articles published between 2010 and 2023. As other inclusion criteria, we used observational and intervention studies in which cirrhotic patients with refractory ascites (defined as refractoriness to diuretics) had received beta-blockers, regardless of which drug, in the treatment of esophageal varices. Systematic reviews and meta-analyses were also part of the evaluation. Studies without full text available and guidelines, editorials or expert opinions were excluded. Initially, based on the determined period of time and the availability of texts, 154 studies were selected. However, after reading the title and abstract and, therefore, applying the exclusion criteria, 20 articles proved to be eligible.

DISCUSSION

After decades of use of beta-blockers as the basis of treatment to reduce the effects of portal hypertension in cirrhotic patients, an article published by Sersté in 2010 raised a question about the use of these agents in patients with cirrhosis and refractory ascites[5]. A prospective observational single-center study was carried out and the effects of NSBB on the survival of 151 patients with cirrhosis and refractory ascites were evaluated. 51% received propranolol for gastrointestinal bleeding prophylaxis. The outcome of the study was that the use of NSBB was associated with increased mortality, given that the average survival of the group using NSBB was 5 months (CI=95%; 3.5–6.5 months), significantly lower than in the group that did not receive NSBB, in which the median survival was 20 months (CI=95%; 4.8-35.2 months; $P<0.0001$). Because it was not a randomized study, the reason why NSBB increased mortality could not be completely understood. However, the authors proposed that the lower blood pressure found in the group treated with propranolol may

partly explain this result, considering that previous studies showed that lower BP was an independent factor for higher mortality[6]. Although Sersté's findings impacted hepatology by questioning the use of such established drugs in a specific clinical context, some reservations regarding his conclusions need to be made. Firstly because it is an observational study, with all the limitations intrinsic to its methodology. Furthermore, the higher mortality in the propranolol group could be explained by a higher level of portal hypertension per se, which would be responsible for larger esophageal varices (an indicator of NSBB prescription). This can be corroborated by the fact that 100% of patients in the propranolol group had esophageal varices, while only 4.1% of patients who did not receive this drug had them. Another limitation to extrapolating the data obtained is the dosage offered to patients in the group treated with NSBB: 46.7% of patients received propranolol at a dose of 160 mg, while other studies carried out with the administration of lower doses of propranolol did not find a worsening of mortality in patients who received the beta blocker[7,8]. Therefore, it can be said that Sersté's contribution is undeniable, as he drew attention to the hypothesis of the "therapeutic window" of beta-blockers in cirrhotic patients[9].

Some studies have been carried out in an attempt to elucidate the hemodynamic effects of NSBB in patients with advanced cirrhosis. One arm of the Sersté study mentioned above found a new harmful association involving these drugs in patients with refractory ascites and the development of post-paracentisis circulatory dysfunction (PPCD)[10]. 10 patients were evaluated before and after discontinuation of NSBB, with a significant reduction in the number of events after drug withdrawal. It is worth noting that PPCD increases the risk of hyponatremia, renal impairment and reduces the probability of survival[11]. Reservations made to the article were the lack of assessment of cardiac dysfunction and the lack of closer follow-up to assess the clinical consequences of PPCD[12]. Another Italian article, however, stated that the slight drop in vascular resistance after paracentesis managed to compensate for the negative inotropic effect of the beta-blocker, so that the supposed explanation for the harmful effects of the drug would have no justification[13].

A German study that included 624 patients concluded that Median Arterial Pressure (MAP) can be an important indicator in patients with decompensated cirrhosis[14]. In the multivariate analysis, beta-blockers were considered a protective factor in 28-day transplant-free survival, but when they analyzed the subgroup with MAP ≤82, the association was not significant, configuring MAP as a reliable parameter to guide the use of NSBB. However, there are several limitations: small interval analyzed, low doses of NSBB and biases common to retrospective studies.

Contrary to the negative conclusions suggested by the study by Serstè's group, Leithead et al. found a beneficial association involving NSBB in patients with advanced liver disease[7]. The conclusion of this retrospective study was that mortality on the liver transplant waiting list was significantly reduced with the use of NSBB, even within the "refractory ascites" subgroup. However, this must be analyzed with caution, given that the clinical condition of patients on the transplant waiting list is unique, with several other systemic complications, in addition to the fact that few data on the individuals' cause of death were presented[15].

A retrospective observational study published in 2016 sought to evaluate the impacts of propranolol use on mortality, risk of hepatorenal syndrome and SBP in patients with different degrees of liver cirrhosis[16]. Propranolol use, compared with no use, was associated with a decreased risk of death in the first 6 months of follow-up, but no impact on mortality thereafter. Furthermore, the effects were dose-dependent: while those who took doses below ≤160 mg/day had a lower risk of mortality compared to those who did not take propranolol, doses >160 mg/day were not related to any beneficial effect on survival. Finally, hepatorenal syndrome occurred in similar proportions between the NSBB vs Non-NSBB groups, but the risk of SBP was significantly decreased in patients using the drug. However, the article does not classify patients as having "refractory ascites", but rather classifies them by the number of paracentesis performed.

Other studies have found beneficial associations involving the use of NSBB in this group of patients. Bossen performed a post hoc analysis of three clinical trials with a total of 1198 patients[17]. Among those

with refractory ascites, mortality was not significantly altered by beta-blocker administration. However, 29% of patients discontinued the use of NSBB, which was associated with a significant increase in mortality. Limitations include the short follow-up time (1 year), lack of HVPG (Hepatic Venous Pressure Gradient) measurement (reinforcing the confounding factor "severity of portal pressure") and a more severe clinical picture among those who discontinued the use of NSBB. Another study followed 316 patients on a liver transplant waiting list[18]. In the subgroup of patients with refractory ascites, there were 34 deaths, of which 6 were in the NSBB group and 28 in the group without. After analysis of a risk propensity score, NSBB were associated with a reduction in mortality. Despite this, the results are not comparable to those of Sersté, as these are studies with different patient profiles and drug doses.

Ngwa published a retrospective cohort with 170 patients on the transplant waiting list[19]. The group did not observe an increase in 90-day mortality or Acute Kidney Injury (AKI) in the subgroup of patients with refractory ascites and using NSBB. The authors suggested that the better survival of decompensated patients in the NSBB group would be due to a better cardiac reserve, that is, a consequence only of their "performance status". In agreement with this, patients who discontinued NSBB (for reasons not explained) continued to have their clinical condition deteriorate with worsening of MELD. Furthermore, overall mortality (after 90 days) was similar between the NSBB x Non-NSBB groups. Therefore, the article suggests that tolerance to beta-blockers is relevant in trying to predict the hemodynamic reserve and consequently the patient's prognosis, at least in the short term. Despite the association with increased survival, NSBB were associated with more stage 1 acute kidney injury, however their group had more chronic kidney disease (CKD), limiting the conclusions. In this study, the use of such drugs was not associated with a reduction in MAP and, in fact, the threshold of 82 mmHg to predict mortality was only useful in the Non-NSBB group. In practice, Ngwa et al. understand that tolerability is a better marker of hemodynamic reserve than MAP. An obvious limitation is that the type and dosage of BB have not been standardized. In practice, the groups for each beta-blocker (carvedilol, propranolol and nadolol) were very heterogeneous, so that making a clinical decision based on this observational study is, to say the least, imprudent.

A real-life multicenter retrospective study found similar results[20]. 740 cirrhotic patients with esophageal varices formed the study population, of which 473 were for primary prophylaxis (PP) and 267 for secondary prophylaxis (SP). With all the caveats natural to observational studies, the results were encouraging, with NSBB treatment reducing mortality in those with moderate to severe ascites in both the PP group ([HR], 0.46; $P<0.01$) and the SP group (HR, 0.56; $P=0.02$). In both the PP and SP groups, the strength of this association was greater with lower doses of propranolol (<80 mg/day).

In 2022, Chen published a retrospective study with a cohort made up only of cirrhotic patients with refractory ascites[21]. The use of propranolol was not only protective in relation to mortality, but also for SBP. Chen and colleagues explained the reduction in mortality by the potential effects of NSBB on the permeability of the intestinal mucosa – through the reduction of portal pressure – and, by extension, on bacterial translocation and systemic inflammation. In our view, this mechanism is not sufficient, as the reduction in systemic inflammation should impact the incidence of hepatocellular carcinoma (HCC), which was similar in both groups. This finding is in line with the results of a retrospective cohort with 107,428 patients, in which Wijarnpreecha et al. found that the incidence of HCC in 100 months was significantly lower in the Beta-blocker group, regardless of the type[22].

Three meta-analyses found no statistically significant association between NSBB use and mortality in cirrhotic patients with refractory ascites. Chirapongsathorn et al.[23], Facciorusso et al.[24] and Wong et al.[25] concluded that there was no positive or negative effect on the risk of death with the use of beta-blockers in this group of patients, in meta-analyses that included observational studies and randomized clinical trials. However, despite their scientific strength, such studies deserve some reservations: for example, Chirapongsathorn was unable to analyze the effect of dose or duration of NSBB use and was unable to differentiate mortality related to hepatic cau-

ses from non-hepatic causes. Facciorusso included studies that lacked individual patient data, such as MELD. The limitations of Wong's publication include the fact that the studies included did not report whether NSBB was being used in primary or secondary prophylaxis or even more consistent data on the type and dose of medications (a problem also reported by Facciorusso). However, it is necessary to understand that the studies in all these meta-analyses were quite heterogeneous, even in Wong's meta-analysis with only observational studies.

Following the same line, a Danish observational study, published in 2015, found no statistically significant association with hospital admission or mortality in the group treated with beta-blockers[26]. However, it should be noted that it was a single-center study, with a small sample (only 61 patients).

A multicenter observational study with a cohort of 718 hospitalized patients with cirrhosis and ascites found no difference in mortality due to the use of NSBB in patients with refractory ascites[27]. When observing the specific criteria recommended by the Baveno consensus, i.e., systolic blood pressure <90 mmHg, serum sodium <130 mEq/L, or presence of acute kidney injury, patients who met any of these criteria were significantly more likely to discontinue the BB than those who did not meet these criteria. Therefore, Bhutta concludes that it is safe to use beta-blockers even in the presence of refractory ascites and that the Baveno consensus was assertive when placing such criteria as limiting the prescription of medications.

More recently, in 2023, Jensen and colleagues published an article based on a database of 1,198 cirrhotic patients, including a sample with refractory ascites, to assess the risk of sepsis[28]. Most patients used propranolol. Those who used NSBB from the beginning of the study had a 1-year risk of sepsis of 5.7% (95%CI 2.8–8.6), whereas patients who did not use it had a risk of 11. 6% (95%CI 7.0–15.9). However, after adjusting for some factors, including restricting the concept of sepsis, the estimate was not statistically significant.

In an attempt to elucidate the pathophysiological mechanisms possibly involved in the increased mortality caused by non-selective beta-blockers, Téllez and collaborators carried out a prospective study in cirrhotic individuals with ascites[29]. Hemodynamic parameters representing systolic function were measured before and after the use of propranolol, indicated in the context of esophageal varices prophylaxis. To this end, the intraventricular ejection pressure difference (IEPD), a reliable parameter for measuring systolic function in patients with decompensated cirrhosis, was evaluated. BBs reduced IEPD in the 20 patients with refractory ascites, but the same was not found in the other group. A lower IEPD was correlated with a drop in renal perfusion pressure. After treatment with NSBB, renal perfusion pressure fell below the renal autoregulation threshold in 55% of cirrhotic patients with refractory ascites, with four meeting criteria for hepatorenal syndrome. An obvious limitation is the small sample size, with only 18 patients with diuretic-responsive ascites and 20 with refractory ascites.

Another study, now with 403 patients with ascites (of which only 16% had refractory ascites), set out to study whether or not the benefits of portal reduction of NSBB compensated for its splanchnic and systemic hemodynamic changes[30]. When using beta-blockers, those decompensated had a smaller drop in portal pressure, but a greater drop in other hemodynamic parameters, such as heart rate and cardiac output. Another important fact is that those decompensated patients who died and who were using NSBB had a lower cardiac output and this was considered an independent predictive factor of the risk of death after a regression model for competing risks. The study also shows that low doses can be equally effective in primary prevention of bleeding, even if decompensated patients have a smaller reduction in portal pressure. Furthermore, it is worth mentioning that there was no correction of important factors that influence hemodynamic parameters. Giannelli found similar results, now having a population of 584 cirrhotic patients on the transplant waiting list[31]. They found an association in those who received NSBB between decreased left ventricular reserve and increased risk of mortality in patients with refractory ascites regardless of the MELD score. Gianelli mentions that it is not possible to know whether the increase in mortality in patients with refractory ascites and using NSBB is due to their previous cardiac impairment or to

an exacerbated response to NSBB that compromises cardiac reserve or even a mixture of the two explanations.

The external validity of such studies is compromised, after all, they are uncontrolled and single-center studies. Furthermore, these three studies have limited measurement time, which prevents conclusions regarding long-term changes in the medications in question. Adherence is an important aspect to consider. However, these three articles leave as a lesson that doctors should be cautious when prescribing NSBB in the context of decompensated cirrhosis in general and that they should closely monitor hemodynamic changes, preferably with non-invasive methods, in their patients.

CONCLUSION

Given the above, it is natural to conclude that doubts regarding the safety of non-selective beta-blockers in patients with refractory ascites still permeate the clinical practice of hepatologists. We believe that the Baveno VII consensus was adequate in this regard. We believe that the decision to use such medications should be individualized. If the decision is in favor of use, regular monitoring of the patient with refractory ascites, with serial analysis of renal function (with electrolytes) and blood pressure, in addition to active questioning of adverse effects, is essential. Low doses of propranolol, that is, less than 160 mg/day, are prudent and, due to the greater risk posed by its extra alpha-adrenergic blocking property and the preliminary results of some studies, carvedilol should be avoided. The question arises to what extent we should postpone the transjugular intrahepatic portosystemic shunt in a patient with recurrent ascites (need for three or more large-volume paracentesis in one year), given that it is also an effective measure in preventing variceal bleeding and does not seems to be so harmful when compared to NSBB. Having made these comments, it is also worth highlighting that the studies discussed throughout the text, despite being all observational - a common limitation among them - are not generally comparable to each other.

Even highlighting negative aspects, the authors recognize that carrying out randomized clinical trials with this very fragile population faces a series of limitations, whether of a moral nature or of a practical nature. In fact, we know that the doubt remains open, and doctors who deal with such patients must pay attention to tolerability and common sense.

Authors' contribution

Maia AG, Palhares LFN, Maia IG and Braulino PDM: data collection and writing of text. Pereira LMMB: Supervisor.

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Maia AG, Palhares LFN, Maia IG, Braulino PDM, Pereira LMMB. Beta-bloqueadores não seletivos em pacientes cirróticos com ascite refratária: onde estamos? Arq Gastroenterol. 2024;61:e23157.

RESUMO – Contexto – O uso consagrado de betabloqueadores não seletivos (BBNS) na prevenção primária e secundária de varizes esofágicas foi recentemente questionado no subgrupo de pacientes com ascite refratária a diurético. **Objetivo –** Analisar criticamente o corpo de evidências sobre a temática a fim de auxiliar decisões clínicas. **Métodos –** Foi realizada uma revisão da literatura nos bancos de dados Pubmed® e Scielo®. No total, 20 artigos entre os anos 2010 e 2023 foram lidos por pesquisadores independentes. **Conclusão –** Ainda permanece duvidoso se o uso de BBNS é deletério nos cirróticos com ascite refratária, no entanto nossa revisão de literatura permite concluir que essas drogas não devem ser proscritas nesses pacientes. Ao contrário, uma decisão médico-paciente pautada na tolerabilidade e em parâmetros hemodinâmicos parece ser uma conduta decerto segura.

Palavras-chave – Betabloqueadores não seletivos; ascite refratária; mortalidade.

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