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Research Article

Evaluation of Patients with Intrapulmonary Shunt without Hepatopulmonary Syndrome at the Hepatology Outpatient Clinic of a Tertiary Hospital in Brazil

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Abstract

Hepatopulmonary syndrome (HPS) is a frequent complication of chronic liver disease and/or portal hypertension. It results from the accumulation of vasoactive mediators by the deficit of hepatic clearance, which causes intrapulmonary vascular dilatation, leading to hypoxia. The diagnosis is made by investigating intrapulmonary shunt plus arterial blood gas analysis with PaO2 lower than 80 in patients with chronic liver disease. It does not have the adequate clinical treatment and can be resolved after liver transplantation. The present study aims to observe, among patients with intrapulmonary shunt without HPS configuration, whether evolution to HPS criteria was observed during follow-up. In a hepatology outpatient clinic of a tertiary hospital in the Federal District were evaluated 93 patients. The intrapulmonary shunt was found in 45 of them, of which 20 did not meet the criteria for HPS. In these patients, a new arterial blood gas analysis was requested after one year to assess whether there was a change in PaO2. Two died from complications of cirrhosis, five were lost to follow-up, and 13 underwent the examination. Of those who experienced the study, three (23%) began to meet the criteria for HPS. In the statistical analysis, there was no statistical significance of the correlation between the variables studied and the outcome of progression to HPS. Conclusion: Patients with a pulmonary shunt may evolve in the follow-up with a reduction in PaO2, being necessary to identify them and adapt them to the best treatment, which may include the use of O2 at home and liver transplantation.

Keywords: Hepatopulmonary Syndrome; Intrapulmonary Shunt; Liver Cirrhosis; Portal Hypertension; Contrast Echocardiography

Abbreviations

SHP: Hepatopulmonary Syndrome; LT: Liver Transplant; NO: Nitric Oxide; PaO2: The Partial Pressure of Oxygen in Arterial Blood; IPVD: Intrapulmonary Vascular Lesions; HBV: Hepatitis B Virus; HCV: Hepatitis C Vírus; EASL: The European Association for the Study on the Liver

Introduction

Hepatopulmonary Syndrome (HPS) is recognized as a significant complication of chronic liver disease and portal hypertension [1], with a prevalence of approximately 10% of patients who are candidates for Liver Transplant (LT) and 5 to 32% of patients with established liver disease [2-4].

HPS manifests due to increased pulmonary circulation of endogenous vasodilating agents, such as nitric oxide (NO), resulting from a deficit in liver detoxification [5]. Because of the accumulation of these agents, a process of dilatation of the intrapulmonary vascular bed arises, with the consequent establishment of pulmonary shunts and hypoxia [4,5]. Studies indicate that intrapulmonary vasodilation can be found in about 40 to 60% of patients with liver disease. Still, only 15 to 30% of these are associated with hypoxemia and meet the criteria for HPS [6].

There are gaps in the literature on the longitudinal follow-up of cirrhotic patients with an intrapulmonary shunt. The percentage of individuals who will meet the criteria for HPS is not precise [1,2].

Recent studies indicate the importance of monitoring and following up these patients through their PaO2 levels by arterial blood gas analysis [7,8]. The HPS graduation refers to the need to use O2 at home if PaO2 is less than 60 mmHg in room air, which is a factor that reflects a greater impairment of the quality of life of these patients, which could impact the follow-up until liver transplantation [3,9,10].

The present study evaluates the evolution of patients with intrapulmonary shunt without HPS configuration.

Materials and Methods

In a hepatology outpatient clinic of a tertiary hospital in the Federal District, 93 patients with liver cirrhosis were selected by convenience sample during one year. The diagnosis of cirrhosis in these patients was previously made through a histopathological study or by a combination of clinical, radiological and laboratory findings. Patients with hepatocarcinoma, active infectious process, hospitalization in the previous 30 days, and those who underwent liver transplantation were excluded from the series.

In these patients, intrapulmonary shunt research occurred accomplished by the end using microbubble echocardiography, which existed considered positive when microbubbles were observed in the left atrium between the fourth and sixth heartbeats in patients considered to have normal cardiac and pulmonary function after imaging and spirometry tests. Arterial blood gas analysis was requested from all who presented with a pulmonary shunt.

The defining criteria for HPS were: the presence of intrapulmonary shunt plus PaO2 in arterial blood gases below 80mmHg or alveolar-arterial gradient > 15mmHg (or >20 if age greater than 64 years) in patients with liver cirrhosis and/or portal hypertension defined by tests imaging and/or liver biopsy.

Patients were classified as mild (PaO2 > 80 mmHg), moderate (PaO2 < 80 mmHg and > 60 mmHg), severe (PaO2 < 60 mmHg and ≥ 50 mmHg) or very severe (PaO2 < 50 mmHg) according to the guidelines of the EASL- The European Association for de the study on the liver.

Statistical analyzes were operated using the Kolmogorov-Smirnov test and Student's t-test in Program R version 4.1.2, and values of $p < 0.05$ were considered significant. Normally distributed data were presented as mean, standard deviation, median, interquartile range for those with non-parametric distribution. Categorical variables were compared by chi squared. Correlation analyzes of parametric data were performed using Pearson's correlation and non-parametric data using Spearman's correlation. A logistic regression model was applied with the presence or absence of HPS as the dependent variable and the clinically relevant variables as independent variables.

Results and Discussion

Of the 93 patients evaluated: 45 had pulmonary shunt on microbubble echocardiography; one of them had an intracardiac shunt (patent foramen ovale) and was therefore excluded; in 37 patients, no shunt criteria were found, and ten patients died or were missed to follow-up. As can be seen in figure 1.

Of the 45 patients with shunt, 24 met the HPS criteria, another 20 had PaO2 greater than or equal to 80 mmHg on arterial blood gases, and one patient was removed for not performing the requested laboratory test.

After one year, of the 20 patients with intrapulmonary shunt and without criteria for HPS, two died from complications of HC, five were missed to follow-up, 13 patients underwent a new blood gas analysis, and clinical-laboratory evaluation was requested.

Of these 13 patients, 10 (76.9%) remained without criteria for HPS and three (23.1%) had criteria to enter the HPS group. Of these, one patient (33.3%) had severe HPS and the two (66.6%) had moderate HPS. Eight (61.6%) were male and five (38.4%) were female. The mean age was 44.61 years. Regarding etiology: five were due to alcohol, three due to autoimmune hepatitis, one due to hepatitis B, one due to hepatitis C, one due to schistosomiasis complications, one due to biliary atresia, and one of undefined etiology, as seen in table 1.

In the statistical model, blood gas analysis_2 was the dependent variable and the others (age, blood gas analysis_1, etiology and gender) were independent variables. In exploratory analysis

gender and blood gas_2 were correlated. In this multivariate linear regression model, the assumptions of homoscedasticity and non-multicollinearity were encountered. Variables were included according to clinical relevance and those that showed correlation between in exploratory analyzes (Table 2, Figure 2). Although not significantly, the worsening of blood gas parameters (gas_2) was associated with the female gender. The large confidence interval suggests that in larger representations this association may be significant.

Portal hypertension exposes the pulmonary vascular endothelium to inflammatory cytokines and stress forces due to high laminar flow. This leads to endothelial dysfunction with a predominantly vasodilating lung disease, HPS [2,11].

Overproduction of nitric oxide and angiogenesis appear to be hallmarks of complicated pathogenesis, leading to intrapulmonary shunt and ventilation-perfusion mismatch [4,5,12].

HPS is characterized by a triad of decreased oxygen saturation in the presence of advanced liver disease and intrapulmonary vascular dilatation [1,13].

In clinical terms, although most patients are asymptomatic, some symptoms may arise, such as dyspnea, platypnea and the orthodeoxia, and the diagnosis is characterized by the presence of a triad that involves: liver disease and/or portal hypertension, arterial oxygenation deficit and dilatations, intrapulmonary vascular lesions (IPVD) with appearance of shunts [2,13-15].

For the detection of intrapulmonary shunt, two tests are fundamental in the investigation: the Contrast Echocardiogram (with microbubbles), a non-invasive exam in which a stirred saline solution is infused intravenously to form microbubbles in the intravascular. In the subsequent evaluation, the diagnosis is established depending on the time it takes for the microbubbles to reach the left atrium, and the presence of microbubbles in the left atrium after 4 to 6 beats, it occurs attributed to the presence of intrapulmonary shunt, and if microbubbles are identified in the first three beats is attributed to an intracardiac shunt [2-4]. A second exam option is pulmonary scintigraphy with macroaggregates with Tc99, useful in the detection of IPVD, since most albumin macroaggregates have a diameter greater than 20 micrometers, that is, larger than the diameter of the usual pulmonary capillary, and thus, they should be impacted on the pulmonary microcirculation under normal conditions, but that in the face of IPVD there is a passage of fractions greater than 6% of the macroaggregates, which is considered the limit of normality. Scintigraphy does not discriminate between cardiac shunt and pulmonary shunt [1,2,16].

The differential diagnosis of hypoxemia with primary pulmonary and even cardiological causes must be carefully performed.

In the present study, of the 93 patients evaluated, intrapulmonary shunt was found in 48.38%, of these 53.3% met the criteria for HPS, showing a high clinical prevalence of the condition in patients with CH. Studies show a prevalence between 4-47% [3,9].

In the group that was followed by an up with a new clinical evaluation and a new arterial blood gas analysis, 23.1% (three patients) now met the criteria for hepatopulmonary syndrome, with PaO2 in the blood gas analysis of 59.4 mmHg, 73.6 mmHg and 79.7 mmHg, respectively, one being considered severe HPS and two with moderate HPS. All were asymptomatic from the respiratory point of view. A study published by França., *et al*. with 16 patients with pulmonary shunt without hypo-oxygenation, after 12 exclusions (11 deaths and one transplant), four patients were followed up with a new microbubble echocardiogram and a new arterial blood gas analysis after 24 months, and not evolved with hypo-oxygenation or shunt resolution [17].

In the group evaluated after an interval of one year, age, PaO2 value of the first arterial blood gas analysis (gas_1), cirrhosis etiology or gender were not correlated with progression to HPS in the three patients who manifested this evolution. In the literature, there is a poverty of data on the longitudinal follow-up of patients with pulmonary shunt without HPS in the context of liver cirrhosis.

Until now, clinical treatment alone has not shown satisfactory results, and on the other hand, after liver transplantation (LT) there are significant regression rates (around 85%) in an interval of 6 to 12 months after the procedure [18,19]. Patients with PaO2 < 50 mmHg and > 60 mmHg in room air are included as a special criterion on the LT list, and those with PaO2 < 50 mmHg may have a contraindication to the procedure, due to the high perioperative risk [4,6,15].

A recent systematic review showed that even in studies that reported high HPS-related mortality, causes of death were mainly attributed to liver dysfunction rather than pulmonary complications [9].

The clinical significance of the presence of the shunt without HPS configuration is not known for sure, so it is significant to moni-

tor this using arterial blood gas analysis instead of pulse oximetry, as this may have an inadequate correlation with PaO2 as demonstrated by Rose, SCP., *et al*. al in a recent article [7].

Knowledge of the natural history of HPS is limited and mainly based on animal models and patients on the list for liver transplantation. Although it is a frequent complication of hepatic disease [20], it can increase the morbidity and quality of life of these patients, in addition to precluding a possible liver transplant in cases of severe hypoxia. Of our evaluated patients, one year after the first examination, three patients (23%) developed hepatopulmonary syndrome. More prospective studies are needed to document the clinical significance of this clinical condition. It is also necessary to standardize the search through screening tests.

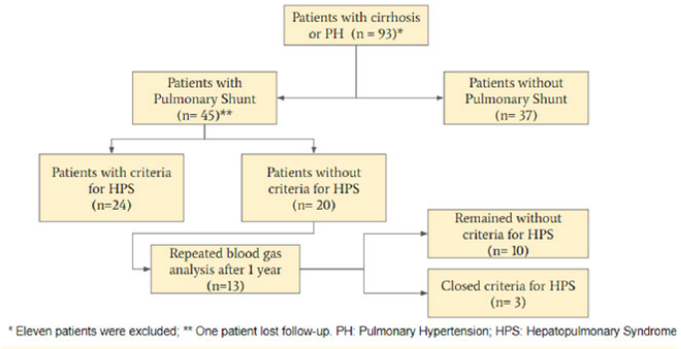

Figure 1: Follow up Flowchart for HSP investigation.

*Eleven patients were excluded: **One patient loss follow-up. PH: Pulmonary Hypertension; HPS; Hepatopulmonary Syndrome

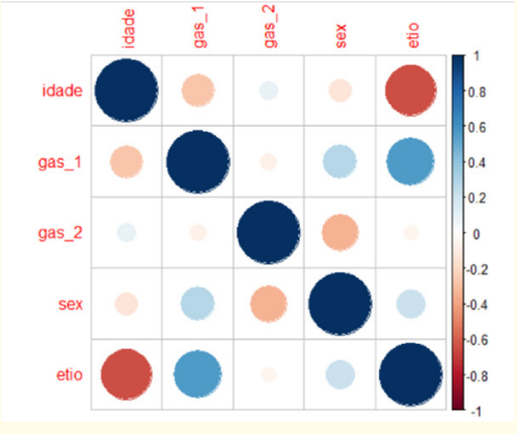

Figure 2: Absence of correlation between the variables studied and the outcome of progression to HPS shown in graph.

Gender	Male: 08 (61,6%) Female: 05 (38,4%)
Age	44,61 years (mean)
Etiology	Alcohol: 05 (38,46%) Autoimmune hepatitis: 03 (23,07%) HBV: 01 (7,69%) HCV: 01 (7,69%) Schistosomiasis: 01 (7,69%) Biliary atresia: 01 (7,69%) Undefined etiology: 01 (7,69%)
HPS graduation	Moderate: 2 (66,6%) Severe: 1 (33,3%)

Table 1: Patients with intrapulmonary shunt without HPS and blood gas analysis after one year. Total patients: 13.

HPS: Hepatopulmonary Syndrome; HBV: Hepatitis B Virus; HCV: Hepatitis C Vírus

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	Estimate Std.	**Std Err.**	**t value**	***p***	**2,5%**	**97,5%**
(intercept)	91,10	35,29	2,58	0,02	18,99	159,07
Age	0,06	0,20	0,32	0,75	-0,28	0,36
Gas_1	0,10	0,41	0,32	0,98	-0,66	0,78
Gender	- 6, 08	4,35	-1,39	0,18	-15,00	2,88
Etiology	0,27	1,22	0,22	0,22	-2,34	2,89

Table 2: Absence of statistical significance of the correlation between the variables studied and the outcome of progression to HPS.

Conclusion

Patients with pulmonary shunt may evolve in the follow-up with a reduction in PaO2, and it is necessary to identify them and adapt them to the best treatment, which may include the use of home O2 and HT. It is fundamental to follow up these patients with pulmonary shunt in the context of liver cirrhosis.

Conflict of Interest

There were no conflicts of interest between the authors of this study.

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