

Liver transplantation in hepatitis delta: South America experience

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Received 22/8/2017
Accepted 16/11/2017

ABSTRACT – Background – The Amazon region is one of the main endemic areas of hepatitis delta in the world and the only one related to the presence of genotype 3 of the delta virus. **Objective** – To analyze the profile, mortality and survival of cirrhotic patients submitted to liver transplantation for chronic hepatitis delta virus and compare with those transplanted by hepatitis B virus mono-infection. **Methods** – Retrospective, observational and descriptive study. From May 2002 to December 2011, 629 liver transplants were performed at the *Walter Cantídio* University Hospital, of which 29 patients were transplanted due to cirrhosis caused by chronic delta virus infection and 40 by hepatitis B chronic mono-infection. The variables analyzed were: age, sex, MELD score, Child-Pugh score, upper gastrointestinal bleeding and hepatocellular carcinoma occurrence before the transplantation, perioperative platelet count, mortality and survival. **Results** – The Delta Group was younger and all came from the Brazilian Amazon Region. Group B presented a higher proportion of male patients (92.5%) compared to Group D (58.6%). The occurrence of upper gastrointestinal bleeding before transplantation, MELD score, and Child-Pugh score did not show statistical differences between groups. The occurrence of hepatocellular carcinoma and mortality were higher in the hepatitis B Group. The survival in 4 years was 95% in the Delta Group and 75% in the B Group, with a statistically significant difference ($P=0.034$). Patients with hepatitis delta presented more evident thrombocytopenia in the pre-transplantation and in the immediate postoperative period. **Conclusion** – The hepatitis by delta virus patients who underwent liver transplantation were predominantly male, coming from the Brazilian Amazon region and with similar liver function to the hepatitis B virus patients. They had a lower incidence of hepatocellular carcinoma, more marked perioperative thrombocytopenia levels and frequent episodes of upper gastrointestinal bleeding. Patients with hepatitis by delta virus had lower mortality and higher survival than patients with hepatitis B virus.

HEADINGS – Hepatitis delta virus. Chronic hepatitis B. Liver cirrhosis. Liver transplantation.

INTRODUCTION

In the world, there are eight virus genotypes in hepatitis delta^(1,2). Type 3 genotype is found in South America, more precisely in the Amazon Basin^(1,2). The Amazon region is one of the areas with the highest prevalence of hepatitis B virus (HBV) and has the highest incidence of hepatitis by delta virus (HDV) in the world⁽³⁾. Superinfection with HDV in an individual with chronic HBV may result, in most cases, in a chronic infection that may lead to the need for liver transplantation (LT)⁽²⁾. There is little information on the evolution of patients with HBV and HDV after liver transplantation⁽⁴⁾. The aim of this study was to analyze the profile, survival and mortality of cirrhotic patients submitted to LT by HDV and compare the results with those found in transplanted patients as a result of mono-infection by virus B.

METHODS

Study design

Retrospective, observational and descriptive study. The Center for Liver Transplantation at the *Walter Cantídio Hospital* (HUWC)

performed 629 transplants between May 2002 and December 2011, of which 29 patients were submitted to LT due to HDV-related cirrhosis (Delta Group) and 40 patients due to chronic mono-infection by the virus of hepatitis B (Group B).

For diagnosis, the recommendations of the Brazilian Health Ministry were defined as the presence of HBsAg or anti-HBcIgM or HBeAg reagents associated with one or more of the following serological markers as a confirmed delta hepatitis case: Anti-HDV total reagent and/or Anti-HDVIgM reagent. Hepatitis B, in cases presenting one or more of the reactive serological markers or molecular biology examination for hepatitis B, such as HBsAg reagent, Anti-HBcIgM reagent, HBeAg reagent, detectable HBV DNA⁽⁵⁾. In our field, the HDV-RNA screening is not readily available.

Variables analyzed

The quantitative variables analyzed were: age, Model for End-Stage Liver Disease (MELD) score, and 5-year survival. The occurrence of thrombocytopenia ($<150,000 \mu\text{L}$) through platelet serum levels was also evaluated in five moments: pre-transplantation, 1st postoperative day (PO), 7th PO, 30th PO and 03 months.

Declared conflict of interest of all authors: none

Disclosure of funding: no funding received

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The qualitative variables of the study were: sex, origin, occurrence of upper gastrointestinal bleeding before transplantation, Child-Pugh classification, occurrence of hepatocellular carcinoma (HCC), and mortality.

Statistical analysis

The statistical significance level was considered for a $P \leq 0.05$. The *t*-Student test was used to evaluate differences between the groups in relation to age and platelet values in the pre-transplantation and 1st PO. To assess the incidence of HCC, Child's classification and the occurrence of upper gastrointestinal bleeding before transplantation, the chi-square test was used. The non-parametric Mann-Whitney test was used to analyze the MELD variables and platelets at the 7th PO, 30th PO and 90th PO. In order to evaluate mortality, the Fischer test was applied. The significance of the difference between patient survival times was assessed with the *logorank* test for two Kaplan-Meyer survival curves. The Statistical Package for the Social Sciences (SPSS), version 17.0 was used for statistical analysis.

Ethics approval

This study was performed according to the ethical standards of data collection and analysis of patients, which were analyzed retrospectively. All data were collected during patient care in the pre-transplant outpatient clinic, in the hospital for the surgical procedure and in the post-transplant outpatient follow-up. This study was approved by the Ethics and Research Committee of *Walter Cantídio* University Hospital and in accordance with the Declaration of Helsinki of 1975.

RESULTS

All patients with HDV are originated from the northern region of Brazil, especially in the state of Amazonas. Patients with hepatitis B were from several regions of Brazil. Men predominated in both groups, being younger in HDV. The evaluation of hepatic function and severity of liver disease were similar between groups. Child-Pugh score was not identified in one patient in the HDV group and six in the HBV group. In the group with HBV, 11 cases did not have MELD identified because they did not use this score to classify the priority for transplantation at the time. The occurrence of upper gastrointestinal bleeding before transplantation did not show statistical difference between groups. Regarding the association of viral infection and the presence of HCC, the HBV group had a higher number of patients with HCC (36.8% vs 17.2%). HBV monoinfected patients presented higher mortality ($n=10$) compared to the Delta Group ($n=1$). The inferential statistical analysis by the *Fischer* test allowed to state that the death incidence was group dependent ($P=0.019$) (TABLE 1).

In relation to the assessment of platelet levels between the groups, there was a statistical difference in the pre-transplantation ($66,428.57 \pm 34,126.27$ vs $102,037.50 \pm 96,823.33 \mu\text{L}$, $P=0.0295$) and in POD 1 (mean $54,222, 86 \pm 27,868.20$ vs $94,063.89 \pm 97,824.87 \mu\text{L}$, $P=0.041$) in favor of a more significant thrombocytopenia in patients with HDV in relation to the HBV Group. After 7, 30 and 90 POD, platelet levels remained lower in the HDV Group, although without statistical significance (FIGURE 1).

In the analysis of survival between groups over a four-year period, patients in the Delta Group had 95% survival and 75% survival in Group B. According to the *logorank* test, using the Kaplan-Meyer survival curves, the observed difference between groups was statistically significant ($P=0.034$). (FIGURE 2).

TABLE 1. Clinical and epidemiological characteristics among transplant patients with hepatitis Delta and hepatitis B

| Variables | Hepatitis delta (n=29) | Hepatitis B (n=40) | P |
|-----------|---|--|---------|
| Age | 33.97 ± 8.68 (22.0-50.0) | 52.93 ± 10.34 (27.0-73.0) | < 0.001 |
| Sex | M = 17 (58.6%) F = 12 (41.4%) | M = 37 (92.5%) F = 03 (7.5%) | 0.001 |
| Child | A = 0 (0.0%) B = 15 (53.6%) C = 13 (46.4%) Missing = 1 | A = 02 (0.0%) B = 17 (50.0%) C = 15 (44.1%) Missing = 6 | ns |
| MELD | 21.2 ± 5.9 | 20.5 ± 4.7 | ns |
| UGB | 12 (41.4%) | 14 (36.8%) | ns |
| HCC | 05 (17.2%) | 14 (36.8%) | 0.051 |
| Mortality | 01 (3.4%) | 10 (25%) | 0.019 |

M: male; F: female; ns: no significance; MELD: Model for End-Stage Liver Disease; UGB: upper gastrointestinal bleeding; HCC: hepatocellular carcinoma.

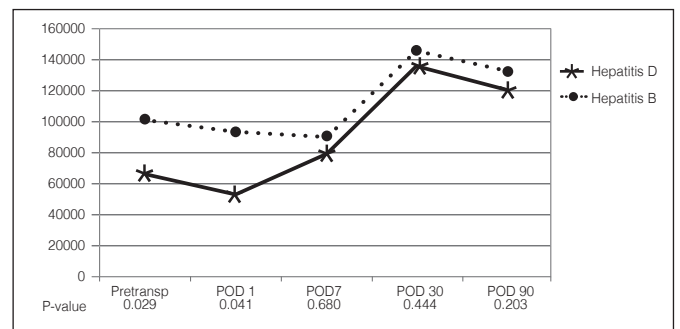


FIGURE 1. Monitoring of platelet levels among transplant patients with hepatitis B and hepatitis delta. Pretransp: pretransplant; POD: postoperative day.

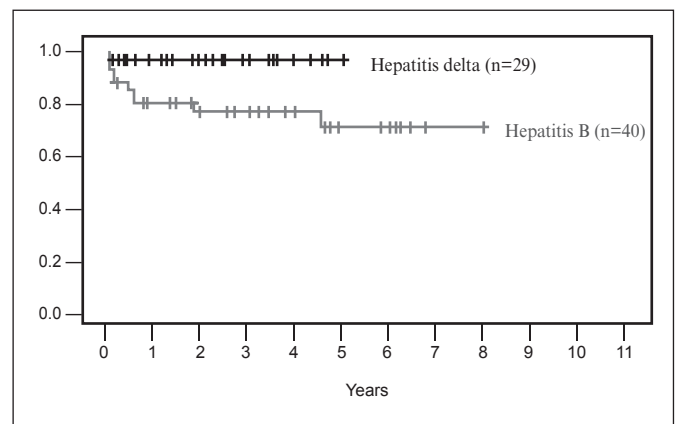


FIGURE 2. Survival of transplanted patients.

DISCUSSION

A study carried out between 1972 and 1997 evaluated 23 patients transplanted due to viral infection by delta hepatitis and showed a long survival⁽⁶⁾. Most studies are conducted in Europe, where there is a predominance of delta virus 1⁽¹⁾ genotype. In this

study, all transplanted patients with chronic hepatitis delta came from northern Amazonas where the predominant genotype is type 3 and mortality was lower than that of patients with HBV.

HDV reaches a higher prevalence between the third and fourth decades of life⁽⁷⁾. The average age of individuals diagnosed with hepatitis D varies between 30 and 44 years old^(8,9). Because hepatitis B is endemic in the Amazon region and often affects individuals in childhood, the disastrous consequences of association with delta virus can be noted in the second decade of life⁽¹⁰⁾. In Brazil, 67.6% of the clinical forms of hepatitis D are chronic⁽⁵⁾.

In 2006, the Brazilian government adopted the MELD score to determine the priority for performing liver transplantation⁽¹¹⁾. The severity scores of MELD and Child did not differ between transplanted patients with HBV and HDV demonstrating that the groups had similar levels of impaired liver function. Among the complications of hepatic cirrhosis, varicose hemorrhage is an important cause of morbidity and mortality among patients. It occurs in 50% to 90% of them being a direct consequence of portal hypertension⁽¹²⁾. It was observed that the two groups had similar levels of upper digestive hemorrhage, with no statistical difference. However, there was a significant occurrence of this complication in each group which shows the risk that these patients have while waiting for a new organ.

A common clinical situation following liver transplantation is the reduction of platelet levels that tend to recover with liver function restoration. A possible cause of thrombocytopenia soon after surgery may be related to platelet consumption due to loss of graft and even sepsis. However, the causes or factors that contribute to persistent thrombocytopenia need better clarification⁽¹³⁾. Severe thrombocytopenia may lead to increased morbidity and mortality related to postoperative hemorrhage⁽¹⁴⁾.

The hepatitis B virus is an established risk factor for the development of HCC⁽¹⁵⁾ and HDV has been associated with high rates of hepatocyte proliferation and oncogenic potential^(16,17). A study with 186 patients with HDV, most with type 1 genotype, showed that 46 patients developed HCC after 83 months of follow-up⁽¹⁸⁾. A British study showed similar prevalence of HCC between groups with HDV and HBV⁽¹⁹⁾. In the present study, the incidence of HCC in the transplanted patients was higher in those who belonged to the HBV

Group in relation to HDV, with results showing borderline or marginal statistical significance ($P=0.0515$). In Brazil, the predominant genotype type 3 seems to be related to the lower number of cases of liver cancer associated with HDV. However, more studies need to be developed to verify the possible difference between genotypes.

One of the largest series involving hepatic transplantation in patients with HDV ($n=76$), identified 88% of survival after 5 years. These results could be related to patients being relatively young and presenting low HBV recurrence rate⁽²⁰⁾. This study showed that patients with HDV had lower mortality and, also, were younger. Some studies suggest that double infection may lead to a better course⁽²¹⁾.

CONCLUSION

Patients with delta hepatitis who were submitted to liver transplantation were predominantly male, coming from the Brazilian Amazon region and with liver function similar to the patients with HBV. They had a lower incidence of HCC, more marked perioperative thrombocytopenia levels and frequent episodes of upper gastrointestinal bleeding. Patients with HDV had lower mortality and higher survival than patients with HBV.

ACKNOWLEDGEMENTS

Thanks to the Surgery Department and post-graduation in surgery of the Federal University of Ceará.

Authors' contributions

Lima DS: conception and design of the study, technical procedures, acquisition, interpretation and analysis of data, manuscript preparation and writing. Murad Júnior AJ: acquisition, interpretation and analysis of data, critical revision. Fernandes GC: acquisition, interpretation and analysis of data, technical procedures. Lima PG: manuscript writing/editing, technical procedures. Coelho GR: conception and design of the study, critical revision, final approval. Barreira MA: technical procedures, manuscript preparation and critical revision. Garcia JHP: conception and design of the study, interpretation and analysis of data, critical revision, final approval.

Lima DS, Murad Júnior AJ, Barreira MA, Fernandes GC, Coelho GR, Garcia JHP. Transplante hepático na hepatite delta: experiência da América do Sul. *Arq Gastroenterol*. 2018;55(1):14-7.

RESUMO – Contexto – A região Amazônica é uma das principais áreas endêmicas da hepatite delta no mundo e a única relacionada com a presença do genótipo 3 do vírus delta. **Objetivo** – Analisar o perfil, mortalidade e sobrevida dos pacientes cirróticos submetidos a transplante hepático por hepatite crônica pelo vírus delta e comparar com os transplantados pela monoinfecção do vírus da hepatite B. **Métodos** – Estudo retrospectivo, observacional e descritivo. Entre maio de 2002 a dezembro de 2011, foram realizados 629 transplantes de fígado no Hospital Universitário Walter Cantídio, dos quais 29 pacientes foram transplantados por cirrose causada pela infecção crônica do vírus delta e 40 pela monoinfecção crônica da hepatite B. As variáveis analisadas foram: origem, idade, sexo, escore de MELD, classificação de *Child-Pugh*, ocorrência de hemorragia digestiva alta e carcinoma hepatocelular antes do transplante, número de plaquetas perioperatória, mortalidade e sobrevida. **Resultados** – O Grupo Delta foi mais jovem e todos oriundos da região Amazônica Brasileira. O Grupo B apresentou maior proporção de pacientes do sexo masculino (92,5%) em relação ao Grupo D (58,6%). A ocorrência de hemorragia digestiva alta antes do transplante, escore de MELD e classificação de *Child-Pugh* não obtiveram diferenças estatísticas entre os grupos. A ocorrência de carcinoma hepatocelular e a mortalidade foram maiores no grupo com hepatite B. A sobrevida em 4 anos foi de 95% no Grupo delta e 75% no Grupo B com diferença estatisticamente significativa ($P=0,034$). Pacientes com hepatite delta, apresentaram mais acentuada plaquetopenia no pré-transplante e no pós-operatório imediato. **Conclusão** – Os pacientes com hepatite por vírus delta submetidos ao transplante hepático eram predominantemente homens, vindos da região da Amazônia brasileira e com função hepática semelhante a dos pacientes com vírus da hepatite B. Apresentavam menor incidência de carcinoma hepatocelular, níveis de trombocitopenia perioperatória mais acentuados e episódios frequentes de hemorragia digestiva alta. Os pacientes com hepatite por vírus delta apresentaram menor mortalidade e maior sobrevida que os pacientes com vírus da hepatite B.

DESCRITORES – Vírus delta da hepatite. Hepatite B crônica. Cirrose hepática. Transplante de fígado.

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