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Retrospective Cohort Study

Primary Liver Transplantation vs. Transplant after Kasai Portoenterostomy in Children with Biliary Atresia: A Retrospective Brazilian Single-Center Cohort

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Abstract

BACKGROUND

Biliary atresia is the most common indication for pediatric liver transplantation, although portoenterostomy is usually performed first. However, owing to the high failure rate of portoenterostomy, liver transplantation has been advocated as the primary procedure for patients with biliary atresia. It is still not clear if a previous portoenterostomy has a negative impact on liver transplantation outcomes.

AIM

To investigate the effect of prior portoenterostomy in infants undergoing liver transplantation for biliary atresia.

METHODS

This was a retrospective cohort study of 42 pediatric patients with biliary atresia who underwent primary liver transplantation from 2013 to 2023 at a single tertiary center in Brazil. Patients with biliary atresia were divided into two groups: those undergoing primary liver transplantation without portoenterostomy and those undergoing liver

transplantation with prior portoenterostomy. Continuous variables were compared using Student's *t*-test or the Kruskal-Wallis test, and categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate. Multivariable Cox regression analysis was performed to determine risk factors for portal vein thrombosis. Patient and graft survival analyses were conducted with the Kaplan–Meier product-limit estimator, and patient subgroups were compared using a two-sided log-rank test.

RESULTS

Forty-two patients were included in the study (25 [60%] girls), 23 undergoing liver transplantation without prior portoenterostomy and 19 undergoing liver transplantation with prior portoenterostomy. Patients with prior portoenterostomy were older (12 vs. 8 mo, *P*=0.02) at the time of liver transplantation and had lower Pediatric End-Stage Liver Disease (PELD) scores (13.2 vs. 21.4, *P*=0.01). The majority of the patients (35/42, 83%) underwent living-donor liver transplantation. The group of patients without prior portoenterostomy appeared to have a higher incidence of portal vein thrombosis (39 vs. 11%), but this result did not reach statistical significance. Prior portoenterostomy was not a protective factor against portal vein thrombosis in the multivariable analysis after adjusting for age at liver transplantation, graft-to-recipient weight ratio, and use of vascular grafts. Finally, the groups did not significantly differ in terms of post transplantation survival.

CONCLUSION

In our study, prior portoenterostomy did not significantly affect the outcomes of liver transplantation.

INTRODUCTION

Population

This was a retrospective, single-center cohort study of patients who underwent LT for BA at Santa Casa de Porto Alegre, Brazil, a tertiary center. Data were extracted from a database of children who underwent LT at our center from 2013 to 2023. Only recipients of primary LT with a diagnosis of BA were selected and divided into two groups: BA without prior PE (no-PE) and BA with prior PE (PE). Demographic and perioperative variables, such as sex, age at LT, PELD score, Model for End Stage Liver Disease (MELD) score, and weight were included in the analysis. Post-LT outcomes, such as vascular and biliary complications, hospital and intensive care unit (ICU) stay, and acute and chronic rejection, were also evaluated. The hospital's ethics committee approved this study.

Liver transplant procedure and follow-up

ABO blood group compatibility determined recipient and donor selection, and no incompatible blood type transplantations were performed during the study period. The grafts were orthotopically implanted using a "piggyback technique." The graft's portal vein was anastomosed in an end-to-end fashion, either to the recipient's portal vein trunk or by interposition of the vascular grafts. In all cases, the hepatic artery was reconstructed using microvascular techniques with 9-0 or 10-0 nylon sutures (Ethicon, Edinburgh, UK). Biliary anastomosis was performed by Roux-en-Y bilioenteric reconstruction.

Tacrolimus (FK 506, Prograf) and steroids were used for immunosuppression in the majority of recipients. Basiliximab (Simulect; Novartis, Basel, Switzerland) was used to induce immunosuppression in the majority of the recipients. Doppler ultrasound was routinely performed on the first postoperative day and, thereafter, according to the clinician's discretion upon clinical assessment. Vascular or biliary alterations upon Doppler ultrasound were confirmed by contrast imaging, either computed tomography or magnetic resonance imaging.

Statistical analysis

Means ± standard deviations and medians (interquartile ranges) were calculated to summarize continuous variables, and the results were compared using Student's *t*-test

or the Kruskal–Wallis test as non-parametric test when distributional assumptions were in doubt. Categorical variables are expressed as numbers and percentages. Differences between groups were assessed using the χ^2 or Fisher's exact test, as appropriate. Patient and graft survival analyses were conducted with the Kaplan–Meier product-limit estimator, and patient subgroups were compared using a two-sided log-rank test. Multivariable Cox regression analysis was performed, adjusting for risk factors. Variables with $P<0.1$ during univariate analysis and those deemed clinically significant were included in the model. The study was reviewed by our expert biostatistician, Gabriele Dell'Era, MD.

MATERIALS AND METHODS

Biliary atresia (BA) is a progressive fibroinflammatory process that leads to obstruction of the biliary tree and cirrhosis if left untreated. It affects people worldwide across ethnicities. BA is the most common cause of pediatric liver-related death and the leading indication for pediatric liver transplantation (LT) [1]. Symptoms are usually present in the first weeks of life, with a pattern of obstructive jaundice and abnormal liver function test results. Early diagnosis and portoenterostomy (PE) are essential for adequate bile flow, clearance of jaundice, and normalization of the serum bilirubin concentration.

Kasai PE is the standard initial procedure for BA, followed by LT for patients for whom PE fails or the condition progresses to liver cirrhosis. Less than 50% of patients with BA undergoing the Kasai PE procedure gain 10 years of transplant-free survival [2]. However, successful PE can increase the life of the native liver, thus postponing the need for LT [3].

Advances in pediatric LT have improved outcomes. A subset of patients with BA benefit from primary LT without first undergoing PE, especially those who are diagnosed at a later stage [4]. PE before 60 days of life is associated with a higher native liver survival rate than PE after 60 days [5]. However, whether prior PE negatively affects LT outcomes in patients with BA remains unclear [6-11]. Here, we aim to add further data on this issue by comparing the outcomes of children with BA who underwent LT without previous PE with those who underwent PE before LT at our institution.

RESULTS

In summary, prior PE did not significantly affect post-LT outcomes in our study. The apparent trend for more PVT events in the no-PE group was probably due to the smaller size and younger age of patients in this group. The post-LT survival did not differ between the groups. Larger multicenter studies are required to confirm our results.

DISCUSSION

LT is primarily indicated for patients with BA in whom initial PE fails or who present with advanced, progressive liver disease at the time of diagnosis. The reported impact of prior PE on LT outcomes differ between studies. A meta-analysis conducted by Wang *et al* did not reveal statistically significant differences in major outcomes, overall survival, and complications between patients undergoing LT with prior PE and those undergoing LT without prior PE [12]. Subsequent studies have not resolved the question [13-16]. Our study did not reveal in survival between the groups.

Kasai PE is performed in an attempt to salvage the native liver and reestablish biliary flow. It yields 10-year LT-free survival in more than 50% of patients with BA. Although the procedure is effective in most cases, adequate biliary drainage is not achieved in approximately 30% of patients, requiring another surgical procedure or LT. Moreover, many long-term complications, such as recurrent cholangitis, portal hypertension,

ascites, infections, gastrointestinal bleeding, and failure to thrive, are observed in those who live with their native liver [17,18].

The present study revealed interesting results in the subgroup of patients who underwent LT without prior PE, including a higher incidence of PVT than in the group who had previously undergone PE. In accordance with the literature, patients with BA who underwent LT without prior PE were younger and smaller in this study. This combination, especially in the setting of LDLT, which was the most common in our cohort, usually results in a higher GRWR, although this difference was not statistically significant in our study. A higher GRWR can lead to large-for-size syndrome, which, in turn, increases the risk of PVT. Patients with BA who undergo LT usually present with sclerotic portal veins that can be replaced with vascular grafts during LDLT to ensure adequate portal flow. However, these same vascular grafts have been associated with PVT after pediatric LDLT [19]. In our cohort, venous grafts were used in 10 (24%) recipients. Similar to the results reported by Neto et al. [19], these grafts were used in a seemingly higher proportion of recipients in the group that developed PVT in our study, although this result was not statistically significant. The PVT subgroup analysis was exploratory in this study and requires validation in larger cohorts.

Excellent outcomes have been reported with LDLT for BA [20,21]. LDLT is considered the first-choice graft in various centers for children with BA, particularly in Asian countries. In accordance with other high-volume centers in Brazil [7], our cohort was mainly composed of children undergoing LDLT (83%). In contrast to Asian countries, deceased donations are widely accepted in Brazil. However, pediatric and adult donors suitable for graft reduction or splitting are scarce, and LDLT is a safe alternative for enlisted patients [22,23].

The early BA diagnosis and the timing to perform the Kasai procedure also influences the decision to indicate a primary LT for BA. A recent European cohort study in BA patients compared early Kasai, late Kasai and primary LT. As expected, native liver survival in 5-y was under 50% (47% early, 30% late Kasai and 4% for those without a portoenterostomy). Overall 5-y survival, however, was quite comparable among the

same groups (91, 83 and 80%, respectively). This study raises an important question as to whether age alone should limit the indication to perform a Kasai procedure. [24]

Lemoine *et al* published their cohort of 113 BA patients submitted to LT. Interestingly, only 14 (12%) underwent a primary LT. In our report, 54.7% of the BA patients underwent a primary LT. This finding may reflect the impact of a late BA diagnosis, precluding the Kasai procedure in developing countries, as in Brazil.[25]

Limitations of the study

The retrospective nature of the study and the relatively small sample are acknowledged as drawbacks. However, survival and posttransplant complication rates in this study were in accordance with those of large transplant centers [19]. Our study might have been underpowered owing to the small size of the cohort. The impact of PE on the outcome of LT remains debatable, and center expertise, especially with LDLT, plays an important role in the outcomes of children with BA. Larger, multicenter studies could help in answering this question.

CONCLUSION

Of the forty-two recipients with BA, 25 (60%) were girls. Living donor LT (LDLT) was the main LT modality (83% of patients). Twenty-three patients were in the no-PE group and 19 in the PE group. Patients in the no-PE group were significantly younger than those in the PE group (8 vs. 12 mo, P=0.02). Patients in the no-PE group had higher PELD scores than those in the PE group (21.4 ± 9.5 vs. 13.2 ± 8.9; P=0.01). The groups did not differ in terms of ischemia times, blood transfusion volume, or hospital and ICU stay. (Table 1).

The no-PE group had a seemingly higher incidence of portal vein thrombosis (PVT) (39% vs. 11%; P=0.07) (Table 2). Although this difference was not statistically significant, we conducted a subgroup analysis on patients with PVT as it might have been clinically significant.

The PVT and no-PVT groups did not reach statistically significant difference in terms of age (8 vs. 10 mo, *P*=0.06) or mean graft-to-recipient weight ratio (GRWR) (4.38 +- 1.20 vs. 3.75 +-1.56, *P*=0.08). The use of vascular grafts as substitutes for the portal vein (cryopreserved deceased-donor iliac vein or living-donor inferior mesenteric vein) also did not reach statistically significant difference between these subgroups (45% vs. 16%, *P*=0.09) (Table 3).

Multivariable Cox regression analysis was performed to evaluate factors associated with PVT. After adjusting for age at LT, GRWR, and vascular grafting, the protective effect of PE was attenuated (Table 4). The 1-year patient and graft survival did not differ between the no-PE and PE groups (91% vs. 84%, *P*=0.4 and 87% vs. 84%, *P*=0.7, respectively) (Figures 1 and 2).

ARTICLE HIGHLIGHTS

Research perspectives

Biliary atresia is the most common indication for pediatric liver transplantation, although portoenterostomy is usually performed first. However, owing to the high failure rate of portoenterostomy, liver transplantation has been advocated as the primary procedure for patients with biliary atresia. It is still not clear if a previous portoenterostomy has a negative impact on liver transplantation outcomes.

Research conclusions

Is there a negative impact of a prior portoenterostomy on liver transplantation outcomes?

Research results

To analyze the post transplant complications and survival in children with biliary atresia with or without a previous portoenterostomy.

Research methods

Retrospective cohort study.

Research objectives

There are no survival differences in patients transplanted with or without a prior portoenterostomy.

There is a trend for more portal vein complications in the group of patients transplanted without a portoenterostomy.

Research motivation

In our study, prior portoenterostomy did not significantly affect the outcomes of liver transplantation.

Research background

Larger studies, also multicenter studies would be important to better address this issue.

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PRIMARY SOURCES

1	João Seda Neto, Paulo Chapchap, Flavia H. Feier, Renata Pugliese et al. "THE IMPACT OF LOW RECIPIENT WEIGHT [≤ 7Kg] ON LONG-TERM OUTCOMES IN 1078 PEDIATRIC LIVING DONOR LIVER TRANSPLANTATIONS", Journal of Pediatric Surgery, 2022 Crossref	109 words — 5%
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