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Review Article

Comparison of liver transplantation outcomes in biliary atresia patients with and without prior portoenterostomy: A meta-analysis

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ABSTRACT

Background: Portoenterostomy is currently the standard first procedure for biliary atresia, and liver transplantation is reserved as a complementary therapy for those with late diagnosis, rapid hepatic decompensation, or failed portoenterostomy. Many previous publications have analysed the impact of prior portoenterostomy on the clinical outcomes of liver transplantation and the conclusions are discordant.
Methods: PubMed and EMBASE were systematically searched for relevant articles, and studies published in Chinese were searched in the Wanfang China Medical Collections. The references of the retrieved studies were also reviewed. In addition, Google scholar was used to further confirm the literature search.
Results: Fourteen studies were included comprising 1560 patients, of which 1190 (76.3%) received portoenterostomy. Meta-analysis did not reveal significant differences in either patient survival rate (odds ratio, 0.82) or graft survival rate (odds ratio, 1.11) over a 5-year follow-up between biliary atresia patients with and without a portoenterostomy procedure prior to liver transplantation; patients who received a prior portoenterostomy procedure had a higher risk of postoperative infection (odds ratio, 2.02).
Conclusion: Accumulated literature suggested that a prior portoenterostomy did not adversely affect outcomes of liver transplantation in children with biliary atresia.

1. Introduction

Biliary atresia (BA), a liver disease with unknown aetiology, is the most common indication for paediatric liver transplantation [1]. Early diagnosis and a timely portoenterostomy (PE) procedure, especially Kasai's PE, are important for a favourable prognosis with the native liver. However, a minority of patients in whom inadequate management leads to an excessively late diagnosis or advanced cirrhosis may be considered for direct liver transplantation.

Studies suggest that PE may achieve immediate biliary drainage among up to 60% of BA patients [2,3]. The long-term outcome of PE has been previously studied and the findings indicate that most of the cases still progress to end-stage liver cirrhosis [4]. Concern has been raised for decades that the prior PE procedure may increase the likelihood of complications for the subsequent liver transplantation [5–7]. For instance, PE may cause abdominal adhesion and increase the difficulty of the recipient's hepatectomy. Also, some patients suffer from recurring cholangitis after PE, which may increase the risk of bacteremia, sepsis, chronic pylephlebitis, and portal vein thrombosis [8].

To evaluate whether a prior PE procedure affects liver transplantation outcomes, we systematically reviewed the literature and performed a meta-analysis. The information may be useful in the informed consent setting, both for the PE itself and for liver transplantation. In addition, the information contributes to the academic debate on the management of BA.

2. Materials and methods

2.1. Literature searches

PubMed (1966–April 2015) and EMBASE (1980–April 2015) were systematically searched by using terms "transplantation"

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and "hepatic or liver" and "biliary atresia" and "portoenterostomy;" studies published in Chinese were searched in the Wanfang China Medical Collections (1990–December 2014) by using the corresponding Chinese terms. Also, the references of the retrieved studies were reviewed. In addition, Google scholar was used to further confirm the literature search. No restriction was made for publication year.

2.2. Study selection and definitions

This systematic review and meta-analysis were conducted based on a pre-specified protocol (the PRISMA Statement) [9]. The titles and abstracts of all relevant studies were scanned independently by two authors (PW and PX). Publications including reviews, case reports, and letters to the editor were excluded. Studies were included if they met the following criteria: (1) the clinical studies involved BA patients with liver transplantation; (2) patients with or without prior PE therapy were included; and (3) patient survival rate, graft survival rate, or incidence of complications including postoperative infection and reoperation were reported or these data can be derived from the presented results.

PE is defined as the original Kasai hepatic PE or any of its variations [10], including any specialized PE such as hepaticoduodenostomy [11] and biliary appendicoduodenostomy [12]. Reoperation after liver transplantation includes re-anastomoses or interventional treatment for vascular thrombosis or stenosis, intra-abdominal haemorrhage and other conditions requiring abdominal exploration within one year after the transplantation. Infection is defined as local or systemic inflammation caused by bacteria, fungi, or viruses.

2.3. Data extraction

Two authors (PW and PX) independently reviewed the literature and extracted the following data from the included studies: first author, publication year, country where the study was conducted, number and age of participants, the ratio of boys to girls, type of liver transplantation, pediatric end-stage liver disease (PELD) score prior to transplantation, operation time, amount of blood loss during operation, rate of reoperation and postoperative infection, and 1- and/or 5-year patient and graft survival rates after the transplantation.

If the required data were not available in the primary article, we contacted the authors and requested *de novo* data. Disagreement on data extraction was resolved by group discussion.

2.4. Statistical analysis

All analyses were performed using STATA statistical software (Version 13.0, STATA Corp, College Station, Texas, US). All statistical tests were two-sided, and a P-value ≤ 0.05 was considered statistically significant, if not otherwise specified.

The 1-year or 5-year survival rate after transplantation was compared between the BA patients with and without prior PE therapy. The odds ratio (OR) and 95% confidence interval (CI) were calculated based on the presented information on outcome of interest, including patient survival rate, graft survival rate, overall complication, and its two main components (i.e., infection and reoperation) by comparing the two groups with and without prior PE therapy. The pooled ORs and 95% CIs were estimated by using a fixed-effects model if the test for heterogeneity across studies was not significant or by a random-effects model if heterogeneity existed. Cochran's Q test was used to determine heterogeneity, and I^2 was computed to assess the degree of inconsistency across studies. Egger's regression asymmetry test was performed to detect any potential publication bias in this meta-analysis. A P-value ≤ 0.10 was considered statistically heterogeneous. In addition, the major complications (i.e., postoperative infection and reoperation) were compared between the two groups with and without prior PE therapy using an approach similar to that used to examine survival rates. Moreover, weighted mean differences (WMDs) and 95% CIs were computed to compare the differences in a few factors (i.e., age, PELD score, transplantation operation time and blood loss during the operation) that may affect the clinical outcomes of liver transplantation between the two groups.

In addition, we stratified the data by study region (e.g., USA vs. non-USA) based on the available data. Sensitivity analyses were conducted to evaluate: (1) if the results were robust to using a fixed- or random-effects model; and (2) if the pooled results were driven by any single study.

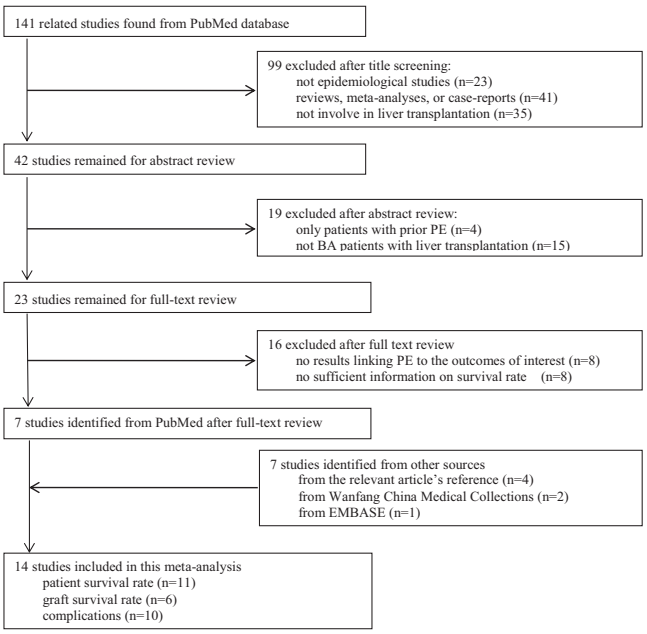

Fig. 1. Flow chart of study screening and selection. BA, biliary atresia; PE, portoenterostomy.

3. Results

3.1. Flow of the included studies

Our literature search resulted in an initial set of 141 publications from the PubMed database. Of these, 118 articles were excluded during title/abstract review due to at least one of the following reasons: (1) they were not epidemiological studies, e.g., studies on mechanism or introduction to PE surgery ($n = 23$); (2) not original studies, e.g., reviews, meta-analyses or case reports ($n = 41$); (3) did not involve liver transplantation ($n = 35$); (4) only included patients with prior PE ($n = 4$); or (5) not BA patients with liver transplantation ($n = 15$). Among the remaining 23 studies, 16 were further excluded after full text screening because of: (1) no results relating prior PE to the outcomes of interest; or (2) insufficient information to retrieve survival rate for either the treatment or control group. Furthermore, seven additional studies were found in other resources, including 4 from the references of the relevant articles [13–16], 2 from the China Medical Collections (Wanfang), and 1 from EMBASE (Fig. 1). Finally, a total of 14 clinical studies were included in the meta-analysis [8,11–23].

Of the 14 included studies (Table 1), 12 were published in English and 2 in Chinese [18,21]. The study populations were from the USA ($n = 6$), China ($n = 3$), Taiwan ($n = 1$), Canada ($n = 1$), France