Pediatr Gastroenterol Hepatol Nutr. 2021 Jul;24(4):366-376
https://doi.org/10.5223/pghn.2021.24.4.366
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Original Article

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Analysis of Cholangitis Rates with Extended Perioperative Antibiotics and Adjuvant Corticosteroids in Biliary Atresia

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OPEN ACCESS

Received: Dec 17, 2020
Revised: Mar 24, 2021
Accepted: May 15, 2021

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: There is no consensus regarding adjuvant therapies following Kasai portoenterostomy (KP) for biliary atresia (BA). This study aimed to analyze the effect of extended perioperative intravenous antibiotics (PI-Abx) and adjuvant corticosteroid on cholangitis and jaundice clearance rates in the 3 years post-KP in children with BA.
Methods: Data of patients who underwent KP between 1999-2018 at a single center were retrospectively analyzed. Group A (1999–2010) received PI-Abx for 5 days, Group B (2010–2012) received PI-Abx for 5 days plus low-dose prednisolone (2 mg/kg), and Group C (2012–2017) received PI-Abx for 14 days plus high-dose prednisolone (5 mg/kg).
Results: Fifty-four patients were included with groups A, B, and C comprising 25, 9, and 20 patients, respectively. The number of episodes of cholangitis was 1.0, 1.6, and 1.3 per patient (p=NS) within the first year and 1.8, 2.3, and 1.7 (p=NS) over 3 years in Groups A, B, and C, respectively. The jaundice clearance rate at 6 months was 52%, 78%, and 50% (p=NS), and the 3-year native liver survival (NLS) rate was 76%, 100%, and 80% (p=NS) in Groups A, B, and C, respectively. A near-significant association was observed between the incidence of cholangitis within the first year and decompensated liver cirrhosis/death at 3 years post KP (p=0.09). Persistence of jaundice at 6 months was significantly associated with decompensated cirrhosis/death at 3 years (p<0.001).
Conclusion: The extended duration of PI-Abx and adjuvant corticosteroids was not associated with improved rates of cholangitis, jaundice clearance, or NLS in patients with BA.

Keywords: Biliary atresia; Cholangitis; Cirrhosis; Antibiotics; Corticosteroids

INTRODUCTION

Biliary atresia (BA) is a fibroinflammatory disorder of early infancy that results in progressive obliteration and obstruction of the extrahepatic and intrahepatic bile ducts [1]. The aim of the Kasai portoenterostomy (KP) procedure is to restore continuity of bile flow; however, the rates of clearance of jaundice after KP are between 40% and 60%, which have not improved over time [2,3]. Progressive biliary fibrosis and cirrhosis occur in most cases, and BA remains the leading indication for liver transplantation (LT) in children [2,3].

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Ascending cholangitis is a frequent complication of BA after KP, and studies have shown that episodes of cholangitis are associated with poor outcomes and native liver survival (NLS) [4]. Hence, protocols in most centers include administration of perioperative intravenous antibiotics (PI-Abx) at the time of KP as well as long-term low-dose antibiotic prophylaxis [5] to minimize the risk of translocation of enteric pathogens to the site of portoenterostomy. However, there remains a distinct lack of evidence-based consensus on treatment with PI-Abx, and institutions around the world have adopted widely differing practices related to the duration of perioperative treatment (ranging from 5 days to 12 weeks) and antimicrobial agent administration, with varying outcomes [6-9].

In addition, some centers use post-KP corticosteroids as adjuncts, and this has shown initial promise in improving the rates of jaundice clearance [7]. Corticosteroids might be effective in reducing the ongoing inflammation that contributes to the progressive biliary fibrosis that is seen in most patients after KP. However, the benefits of post-KP corticosteroids remain debatable, and this practice has not been universally adopted [10].

At our center, the treatment protocol for BA has undergone a series of revisions and modifications over the years, based on available evidence and best practices. Prior to 2012, patients with BA who underwent KP received intravenous (IV) antibiotics for 5 days immediately after surgery. Since 2012, the protocol has been modified to increase the duration of post-KP IV antibiotics to at least 14 days based on the experiences and results of centers that adopted prolonged administration of PI-Abx in their post-KP medical management protocol [6,8,9]. Post-KP corticosteroid treatment has been incorporated into the protocol since 2010 [11]. The hypothesis was that the overall short-term and long-term outcomes of BA might improve with the implementation of these progressive changes.

The aim of this study was to examine the effect of increasing the duration of administration of PI-Abx and corticosteroids on the rates of cholangitis in the first 3 years after KP, rate of clearance of jaundice, and survival outcomes in children with BA.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients who were diagnosed with BA and underwent KP between 1999 and 2017 at KK Women's and Children's Hospital in Singapore. Cases were identified from the department's BA database. BA was suspected based on the findings of acholic stools and conjugated hyperbilirubinemia in a young infant and confirmed by liver histology and intraoperative findings or cholangiogram at the time of KP. Patients who did not undergo KP but underwent primary LT were excluded from the study.

Patients were divided into three groups based on their treatment with PI-Abx and corticosteroids at different time periods. Group A comprised patients who underwent KP between 1999 and 2010 when perioperative IV ceftriaxone (50 mg/kg/day) or IV cefazolin (150 mg/kg/day) was administered for 5 days. Group B comprised patients who underwent KP between 2010 and 2012, who also received perioperative IV ceftriaxone for 5 days, plus postoperative low-dose oral prednisolone (2 mg/kg) which was started on postoperative day (POD) 5 and weaned over one month. Group C comprised patients who underwent KP between 2012 and 2017 when the revised protocol consisted of perioperative IV piperacillin-tazobactam (100 mg/kg q8h) given for at least 14 days post-KP along with postoperative high-dose oral prednisolone (5 mg/kg)

https://doi.org/10.5223/pghn.2021.24.4.366

initiated on POD 5 and weaned over one month. The data of patients who received antibiotics for longer than the intended duration because of acute indications such as cholangitis or other infections were analyzed according to their original assigned groups on an 'intention-to-treat' basis. All patients received prophylactic oral cotrimoxazole for at least 1-year post-KP. Patients also received medium-chain triglyceride (MCT)-enriched formula, ursodeoxycholic acid, and fat-soluble vitamin supplementation as standard treatment in all three groups; additional MCT supplementation was provided to infants who were breastfed.

The primary outcome measure was the number of episodes of cholangitis in the first 3 years after KP. The secondary outcomes were clearance of jaundice at 6 months, Pediatric End-stage Liver Disease (PELD) score, decompensated liver cirrhosis, and NLS at 1 and 3 years post KP.

Cholangitis was defined as the presence of systemic inflammation (fever >38°C or elevated inflammatory markers, such as the white blood cell count and C-reactive protein level), with evidence of cholestasis or abnormal results on liver function tests, with an alkaline phosphatase level, γ-glutamyltransferase level, aspartate aminotransferase level, or alanine aminotransferase level >1.5 times the upper limit of the respective normal ranges and/or elevation of these liver enzyme levels from the baseline levels, in accordance with the Tokyo Guidelines [12]. Cholangitis that occurred within 1 month after KP was classified as "early cholangitis." Cases of cholangitis with positive blood cultures were categorized as culture-proven cholangitis, whereas cases of cholangitis with negative blood cultures were categorized as culture-negative cholangitis cases. Multidrug-resistant organisms (MDROs) were defined as organisms that were non-susceptible to two or more classes of antimicrobial agents [13]. Jaundice clearance was defined as a total serum bilirubin level of <20 μmol/L within 6 months after KP. The PELD score was calculated based on serum bilirubin levels, international normalized ratio, serum albumin levels, age, and growth failure [14]. Decompensated cirrhosis was defined in this study as the development of at least one or more complications such as variceal hemorrhage, ascites, encephalopathy, and/or significant impairment of synthetic function (hypoalbuminemia <25 g/L, prothrombin time >20 seconds) [15].

The data collected included patient demographics, age at KP, results of liver biochemistry and microbiologic studies, and outcomes such as LT or death. Data analysis was performed using IBM SPSS Statistics for Windows, version 19 (IBM Co., Armonk, NY, USA). Continuous variables were expressed as median (range) or mean±standard deviation, while categorical variables were expressed as numbers (percentages). Comparisons were performed with Group A as the historical control; the Mann–Whitney U-test was used for non-parametric continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables. Survival functions were expressed using the Kaplan–Meier survival curves. Differences were considered statistically significant at $p<0.05$.

The study was approved by the Singhealth Centralized Institutional Review Board (reference number 2019/2237). Waiver of informed consent was approved as no patient identifiers were collected.

RESULTS

In total, 54 (32 male, 22 female) out of 56 patients with BA underwent KP during the study period, with a median follow-up period of 4 years (range, 1–18 years). Two patients were

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Table 1. Comparison of baseline characteristics between groups A, B, and C

Variable	Overall (n=54)	Group A (n=25)	Group B (n=9)	Group C (n=20)
Median age at KP (d)	52	53 (32–109)	49 (42–119)	52 (29–97)
Sex (% male)	30 (56)	13 (52)	5 (56)	12 (60)
Prematurity <36 weeks gestational age	1 (2)	1 (4)	0	0
Other congenital anomalies	2 (4)	2 (8)	0	0
Anatomic type of BA	Type 3 (100)	Type 3 (100)	Type 3 (100)	Type 3 (100)
INR	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
Albumin (g/L)	34 (30–38)	35 (30–38)	34 (31–37)	34 (30–36)
Direct bilirubin (μmol/L)	99 (55–142)	86 (55–108)	111 (66–142)	100 (65–136)
Total bilirubin (μmol/L)	147 (109–190)	145 (109–180)	147 (115–187)	150 (121–190)
Gamma-glutamyl transferase (U/L)	662 (76–1,219)	491 (76–983)	848 (128–1,219)	647 (213–1,012)
Alanine transaminase (U/L)	132 (17–441)	153 (17–441)	154 (67–289)	89 (50–220)
Aspartate transaminase (U/L)	160 (36–391)	177 (40–302)	140 (36–391)	162 (82–391)

Values are presented as median (range) or number (%).
Group A (1999–2010) received perioperative intravenous antibiotics (PI-Abx) for 5 days, Group B (2010–2012) received PI-Abx for 5 days plus low-dose prednisolone (2 mg/kg), and Group C (2012–2017) received PI-Abx for 14 days plus high-dose prednisolone (5 mg/kg).
KP: Kasai portoenterostomy, BA: biliary atresia, INR: international normalized ratio.

excluded due to primary LT. No patient was lost to follow-up. Group A comprised 25 patients, Group B comprised 9 patients, and Group C comprised 20 patients. Two patients in Group A had concomitant congenital cardiac anomalies. No patient had splenic malformation. The baseline characteristics were comparable across the three groups (**Table 1**). All the patients were surgically classified as having type 3 BA. There were no postoperative surgical complications such as intestinal perforation, anastomotic breakdown, or wound infection in our cohort.

Overall, 39 (72%) patients developed at least one episode of cholangitis within the first 3 years after KP. All three groups showed the highest incidence of cholangitis in the first year, which subsequently decreased over the following 2 years (**Fig. 1**). The overall rate of cholangitis was 1.3±1.4 episodes per patient within the first year and 1.8±2.3 episodes per patient over 3 years. Using Group A as the historical control group (1.0 cholangitis episode per patient), on comparison, the mean number of episodes of cholangitis per patient within the first year showed no difference between Groups A and B (1.0 vs. 1.6, p=0.26) or Groups A and C (1.0 vs. 1.3, p=0.49). Similarly, no significant difference was observed in the mean cholangitis rate per patient over 3 years between Groups A and B (1.8 vs. 2.3, p=0.46) and Groups A and C (1.8

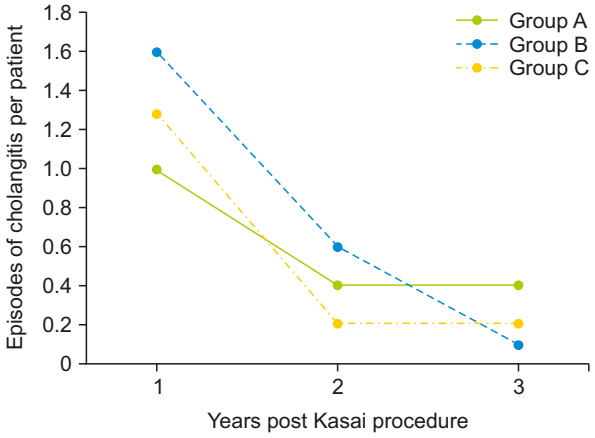

Fig. 1. Incidence of cholangitis in the first 3 years post Kasai portoenterostomy. Group A (1999–2010) received perioperative intravenous antibiotics (PI-Abx) for 5 days, Group B (2010–2012) received PI-Abx for 5 days plus low-dose prednisolone (2 mg/kg), and Group C (2012–2017) received PI-Abx for 14 days plus high-dose prednisolone (5 mg/kg).

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vs. 1.7, p=0.88). There was no significant difference in the rates of early cholangitis (<1-month post-KP) between Groups A and B (20% vs. 0%, p=0.26) or Groups A and C (20% vs. 35%, p=0.15). There was also no significant difference in the proportions of patients who were cholangitis-free (zero episodes of cholangitis) in the first 3 years (32% [n=8] in Group A, 33% [n=3] in Group B, and 20% [n=4] in Group C).

Among the cases of cholangitis, 13 cases (11%) were culture-proven, with the most common pathogen being *Klebsiella pneumoniae* (n=6, 46%). The second most common organisms were *Enterococcus faecalis* (n=2, 13%) and *Pseudomonas aeruginosa* (n=2, 13%). There were no cases of MDRO detected in Groups A and B, whereas in Group C, 5 out of 20 patients had reported infections with MDRO. Multidrug-resistant (MDR) infections emerged relatively early at a median duration of 3 months (range, 1-6 months) post-KP. Patients with MDR infections had extended-spectrum beta-lactamase (ESBL)-producing *K. pneumoniae* in their bloodstream, which were resistant to all penicillins, cephalosporins, and aminoglycosides. Patients received IV meropenem between 14 and 21 days, and all 5 patients showed negative repeat blood culture results after treatment, with no recurrence of MDR infections thereafter. However, all patients exhibited signs of progressive liver disease with decompensated cirrhosis within 2 years of follow-up, one of whom had already undergone LT at 2 years of age.

The 6-month rate of clearance of jaundice in Group A was 52% (13/25); in comparison, jaundice clearance was achieved in 7 out of 9 patients (78% vs. 52%, p=0.18) in Group B, and 10 out of 20 patients (50% vs. 52%, p=0.89) in Group C. At 3 years after KP, the number of patients with decompensated cirrhosis was 7 (28%), 0 (0%), and 7 (35%) in Groups A, B, and C, respectively. There was no significant difference in the 6-month rate of clearance of jaundice between the patients who received corticosteroids (group B+C) and those who did not receive corticosteroids (group A) (59% vs. 52%, p=0.63). Overall, 11 (20.4%) patients underwent LT at a median age of 3 years. There was no significant difference in the rate of NLS at 1-year post-KP between Group A (100%), B (100%), and C (95%) or at 3 years post-KP between Group A (76%), when compared with group B (100% vs. 76%, p=0.11), and Group C (80% vs. 76%, p=0.75). A comparison of PELD scores between the three groups at 1 year and 3 years post-KP as well as the Kaplan–Meier survival curve for NLS are shown in **Fig. 2**.

Based on the results of the univariate analysis, the persistence of jaundice at 6 months (p<0.001) and the incidence of cholangitis within the first year (p=0.09) were associated with statistically significant or near-significant higher odds of decompensated liver cirrhosis or death (**Table 2**). The results of logistical regression performed to ascertain the effects of jaundice clearance and the incidence of cholangitis on the likelihood of decompensated liver cirrhosis or death showed no statistical significance. The mean number of episodes of cholangitis within the first year in those who developed decompensated cirrhosis or those who died was 1.4, compared to 1.1, as seen in those who were alive without decompensated

Table 2. Univariate analysis of the risk factors for decompensated liver cirrhosis or death

Risk factor	Odds ratio (95% CI)	Chi squared p-value
KP >60 days	1.1 (0.3–3.5)	0.91
KP >90 days	2.5 (0.5–8.4)	0.27
Lack of jaundice clearance at 6 months	4.0 (2.3–6.8)	<0.01
Use of postoperative steroids	0.9 (0.5–1.6)	0.74
Cholangitis within first year post-KP	4.0 (0.8–20)	0.09

KP: Kasai portoenterostomy, CI: confidence interval.

https://doi.org/10.5223/pghn.2021.24.4.366

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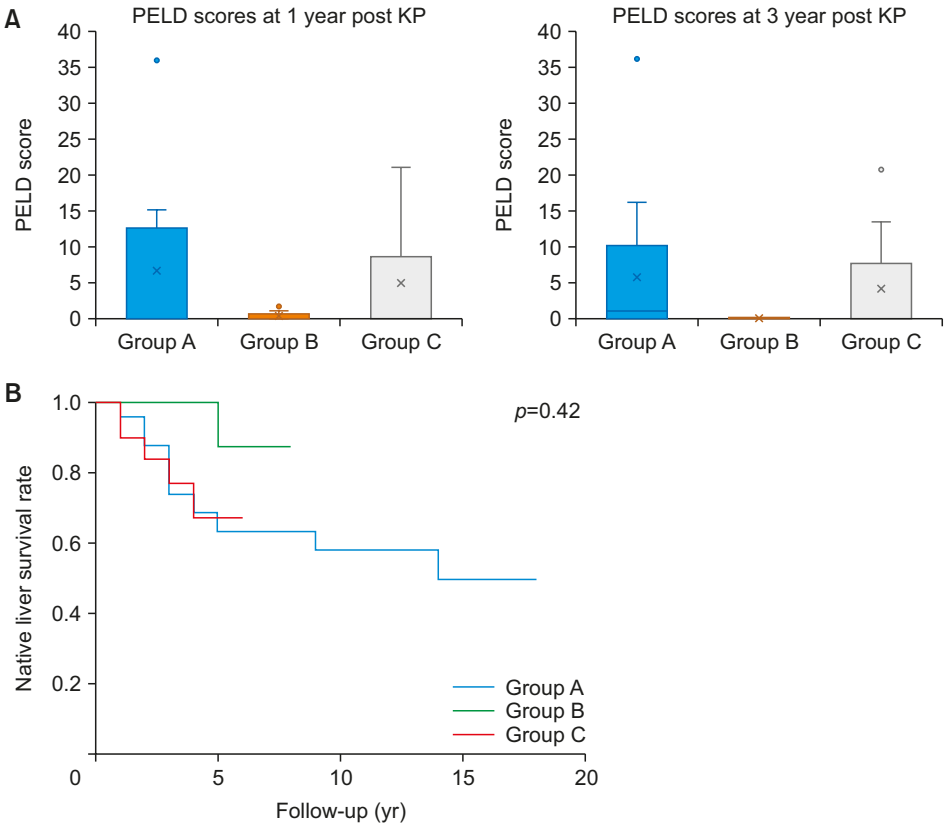

Fig. 2. (A) Pediatric End-stage Liver Disease (PELD) scores at 1 and 3 years post Kasai portoenterostomy (KP). (B) Kaplan–Meier survival curves comparing native liver survival rates between groups A, B, and C. Group A (1999–2010) received perioperative intravenous antibiotics (PI-Abx) for 5 days, Group B (2010–2012) received PI-Abx for 5 days plus low-dose prednisolone (2 mg/kg), and Group C (2012–2017) received PI-Abx for 14 days plus high-dose prednisolone (5 mg/kg).

cirrhosis (p=0.50). Similarly, the mean number of episodes of cholangitis at the end of 3 years in those with decompensated cirrhosis or those who died was 1.9 versus 1.4 in those who were alive without decompensated cirrhosis (p=0.49) (**Table 2**).

There were no reported short-or long-term adverse effects from the use of postoperative corticosteroids in our cohort.

DISCUSSION

Our study demonstrated that an extended duration of administration of PI-Abx from 5 days to 14 days did not result in an improvement in the rate of cholangitis, liver function, or rate of NLS in the first 3 years after KP. While the outcomes of BA throughout the world have been well reported in the literature, to the best of our knowledge, our study was the first to specifically examine the effect of the duration of administration of PI-Abx during KP on the rate of cholangitis.

We selected the cholangitis rate as the primary outcome measure because many studies have shown that the overall outcome of BA is influenced by the frequency of cholangitis [16-21]. Moreover, cholangitis might be associated with significant morbidity requiring prolonged

https://doi.org/10.5223/pghn.2021.24.4.366

hospital stay and resulting in increased healthcare costs [22]. Our study also showed a near-significant association between cholangitis in the first year post-KP and progression of liver disease, and a trend towards a higher frequency of cholangitis in patients who had poorer outcomes with KP for BA, although this trend was not statistically significant because of the small sample size. Nonetheless, the prevention and aggressive treatment of cholangitis remain the cornerstones in the management of BA. The use of PI-Abx for the prevention of early cholangitis after KP is adopted almost universally; however, the type of PI-Abx and duration of administration of PI-Abx vary from center to center. For example, Meyers et al. [6] reported the use of PI-Abx for 8-12 weeks, Petersen et al. [8] reported the use of PI-Abx for 3 weeks, and Stringer et al. [7] reported the use of PI-Abx for 5 days, while Japanese centers opted to administer PI-Abx until the serum levels of C-reactive protein normalized [9]. No data on the rates of cholangitis were available from these studies. Instead, these studies reported the 6-month rate of clearance of jaundice, which is widely recognized as an important prognostic factor in BA [23-25]. Studies [7,26] in which short courses of PI-Abx (5 days) were administered reported rates of clearance of jaundice of 47–76%, while those in which longer courses of PI-Abx were administered (3–12 weeks) [6,8,9] reported 30–81%. clearance of jaundice. These findings are comparable to the results in our study wherein the rates of clearance of jaundice in patients who received a short course of PI-Abx was 52% compared to the 50% rate noted in those who received 2 weeks of PI-Abx. While we acknowledge the heterogeneity of different study cohorts, our study provides additional evidence that an extended duration of administration of PI-Abx is not associated with an improvement in the rate of clearance of jaundice.

Consistent with other studies, we found that most episodes of cholangitis occurred within the first 12 months after KP [27,28]. In addition, the rate of culture-proven cholangitis in our cohort (11%) was similar to the rate (9.5%) reported by Wu et al. [28]. Causative organisms, namely the Enterococci species, *K. pneumoniae* and *P. aeruginosa*, have also been reported in epidemiological studies of cholangitis [29]. We observed an increased incidence of MDRO in recent years (Group C) compared to that in earlier periods. While this could be a cohort effect attributable to increased surveillance and detection in the recent years, the association between prolonged broad-spectrum antibiotic use and the increased incidence of antibiotic resistance cannot be entirely dismissed. MDRO are becoming a major public health problem; hence, it is important to avoid the unnecessary use of antibiotics.

Based on the results of our study, an extended 14-day course of PI-Abx did not lead to a significant improvement in the short-to-medium-term outcomes in BA. This finding must also be balanced against the morbidity of prolonged hospital stay, complications from IV access, and the potential risk of MDR infections.

The 6-month rate of clearance of jaundice since the inclusion of postoperative corticosteroids in our study cohort also showed no improvement, and the proportion of infants who achieved clearance of jaundice at 6 months was similar between the two groups. This is similar to the findings reported in a recent Cochrane meta-analysis 2018 [10], which showed no difference in the rate of jaundice clearance between corticosteroid and non-corticosteroid-treated patients (relative risk 0.89; 95% confidence interval [CI] 0.67–1.17). The Cochrane meta-analysis also reported that postoperative corticosteroids did not improve the long-term NLS of patients. In addition, the Steroids in the Treatment of Biliary Atresia (START) trial [30] reported no improvement in NLS with the rate being 58.7% in the corticosteroid group vs. 59.4% in the placebo group (adjusted hazard ratio, 1.0 [95% CI, 0.6 to 1.8]; p=0.99) at 24

https://doi.org/10.5223/pghn.2021.24.4.366

months of age. Another American National Database study [31] with a large sample size also did not show any benefit of corticosteroids on NLS. Davenport et al. [11] also showed that patients who received postoperative corticosteroids had improved jaundice clearance, but no showed difference in NLS or the need for transplantation (12% versus 13%, p=0.99) at 6 months and 12 months (26% versus 35%, p=0.47). Another meta-analysis showed that corticosteroid therapy improved jaundice clearance, especially in infants who underwent KP by 70 days of age; however, it lacked data on the NLS rate [32]. This short-term effect of improved jaundice clearance was not observed in our study cohort. Although we did not observe any detrimental effects of corticosteroids in our population, the use of postoperative corticosteroids needs to be weighed against the risk of corticosteroid-related adverse events. The unremarkable safety profile of corticosteroids has also been reported previously [33,34]. In contrast, the START trial reported earlier development of serious adverse events with corticosteroid use [30], and Alonso et al. [35] described impaired length, weight, and head circumference growth trajectories in children who underwent corticosteroid therapy post-KP.

In our cohort, the inclusion of adjuvant corticosteroids after KP showed a trend toward significance in improving PELD scores and NLS rates at 1 and 3 years post-KP for the initial two years after implementation (Group B); however, subsequently did not show statistically significant changes in the PELD scores in the subsequent cohort (Group C) that received extended PI-Abx and high-dose corticosteroids. We are cautious about drawing any firm conclusions based on these results, as Group B represented a very small number of patients over a relatively short study period. Further studies are necessary to determine whether corticosteroids have a significant impact.

The three-year NLS rate in our population appeared to be higher than that reported by other centers. For example, McKiernan et al. [36] reported a 3-year NLS rate of 61% in the studies conducted in the United Kingdom and Ireland. This was most likely due to the lower transplantation rate in the local setting. In Singapore, there is a relatively low rate of organ donation, and pediatric LT is usually performed using living donor grafts. These factors were likely to influence the selection of patients for transplantation, with fewer patients receiving LT at an early age. Hence, we analyzed other surrogate outcomes, such as decompensated cirrhosis and PELD scores, to reflect the true severity and progression of liver disease in our cohort.

Overall, there is still no consensus [37,38] regarding adjuvant therapies post-KP, but with additional emerging evidence, clinical practice and institutional protocols previously established should be constantly re-evaluated. There has been recent interest in other adjuvant agents such as IV immunoglobulins, although early results suggest that their efficacy is limited [39].

Based on the findings of this study, we have discontinued the prolonged administration of PI-Abx with broad-spectrum piperacillin-tazobactam and have modified the protocol to administer IV cefotaxime for only 5 days since 2018. We have maintained the use of corticosteroids in our protocol and will review its efficacy in our patients in the future.

This study had several limitations. First, this was a retrospective single-center study using historical control over a long study period, with inherent limitations of ascertainment and verification bias. Second, the small sample size and segregation of our study population into three groups based on protocol changes affected the quality of the statistical analysis. Third, our study would not be able to provide evidence on the effect of a further increase in duration

(for example, >14 days) of administration of PI-Abx, although we postulate that this would be unlikely to have a significant benefit in the overall outcome. The main strength of the study was the high rate of follow-up that allowed us to achieve consistent and comprehensive data collection over a long study period.

In conclusion, extended duration of administration of PI-Abx for 14 days and adjuvant corticosteroids were not associated with improved rates of cholangitis, jaundice clearance, and NLS at 3 years post-KP. The increasing incidence of early antibiotic resistance in recent years is a growing public health concern and underscores the need for vigilant antimicrobial stewardship.

ACKNOWLEDGEMENTS

We would like to acknowledge the clinical contributions and support of the multidisciplinary Gastroenterology, Hepatology and Nutrition, and Hepatobiliary Surgery teams at KK Women's and Children's Hospital in managing and looking after the children with chronic liver disease as well as their families.

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