Effect of combined ursodeoxycholic acid and glucocorticoid on the outcome of Kasai procedure
A systematic review and meta-analysis

Jian-Li Qiu, MD, PhD, Ming-Yi Shao, MD, PhD, Wen-Fang Xie, MD, PhD, Yue Li, MD, PhD, Hai-Die Yang, MD, Min-Min Niu, MD, Hua Xu, MD, PhD

Abstract

Introduction: Multiple studies have investigated the effect of ursodeoxycholic acid (UDCA) or glucocorticoid (GC) on the outcome of the hepatopancreaticoenterostomy (Kasai procedure) in patients with biliary atresia (BA). However, the combined effect of these drugs (UDCA + GC) is little understood.

Methods: This meta-analysis specifically evaluated the effect of UDCA + GC after the Kasai procedure in patients with BA. A comprehensive literature search was conducted for all relevant articles in the electronic databases Medline, PubMed, Cochrane, Excerpta Medica Database (EMBASE, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database on Disc (CBM-disc), and Vendor Information Pages (VIP).

Results: Eight studies with BA patients were finally included in our meta-analysis. The 8 identified studies consisted of 3 case-control, 3 cohort, and 2 randomized controlled trials (RCTs) with overall 530 subjects (144, 152, and 234 subjects, respectively). Among them, 312 patients were treated with UDCA + GC, while 218 received placebo or other intervention. The meta-analysis indicated that groups that received UDCA + GC had significantly lower rates of postoperative jaundice relative to the controls (pooled, odds ratio OR = 2.41; 95% confidence interval CI = 1.44-4.04; Z = 3.34; P = .0008), while rates of cholangitis were similar (pooled, OR = 0.87; 95% CI 0.43-1.74; Z = 0.40; P = .69).

Conclusions: Combined UDCA and GC intervention was superior to that of the control in accelerating the clearance of serum bilirubin in patients with BA after the Kasai procedure. However, this conclusion requires further confirmation using RCTs of high methodological quality.

Abbreviations: BA = biliary atresia, CBM-disc = Chinese Biomedical Literature Database on Disc, CI = confidence interval, CNKI = China National Knowledge Infrastructure, GC = glucocorticoid, LT = liver transplantation, OR = odds ratio, RCT = randomized controlled trial, RR = relative risk, UDCA = ursodeoxycholic acid, VIP = Vendor Information Pages.

Keywords: biliary atresia, glucocorticoid, hepatopancreaticoenterostomy, ursodeoxycholic acid

1. Introduction

Biliary atresia (BA) is a common hepatic disease affecting only neonates and infants.[1] The main characteristics of BA are chronic proliferative cholangitis, liver cirrhosis, and terminal hepatopathy, resulting from progressive obstruction of the intrahepatic and extrahepatic bile duct.[2] However, its pathogenesis is still not very clear. Current studies mainly focus on viral infection, chronic inflammation, autoimmune bile duct injury, and bile duct malfunction. Viruses under consideration include rotavirus, reovirus, and cytomegalovirus.[3]

Currently, the Kasai procedure (i.e., hepatopancreaticoenterostomy) is used to treat BA, but its success rate is variable and influenced by several factors, including age. Older infants (especially >90 days) have a worse outcome with reduced survival rates of autologous liver.[4,5] Survival rates are reportedly improved by administration of glucocorticoid (GC) to reduce inflammation, ursodeoxycholic acid (UDCA) to relieve jaundice,[6] and antibiotics to prevent cholangitis. However, clinical studies to evaluate the outcome of these interventions indicated that application of GC or UDCA separately was not superior to control treatments.[6]

A meta-analysis showed that high dosage of GC improved jaundice clearance after the Kasai procedure,[7] and combined treatment of UDCA and GC may provide a better outcome.[8,9] Thus, to understand the effects of combined UDCA and GC on
postoperative outcomes of the Kasai procedure in patients with BA, the present systematic review of case-control, cohort, and randomized controlled trial (RCT) studies was undertaken.

2. Methods

2.1. Ethical review

All the clinical trials included in the present study were approved by the Institutional Review Board.

2.2. Selection of studies

All relevant clinical trials were included, irrespective of randomization, blindness of design, language, year, or status of publication. Only patients with BA were considered. Studies using combined application of UDCA and GC (UDCA+GC) as the main intervention, at any dose, relative to placebo or no intervention (control) were considered. An adjuvant therapy regimen was allowed, as long as the control group received a similar intervention.

The outcome measures essential for selection were postoperative levels of serum bilirubin and percentage of patients with cholangitis. Moreover, all included trials had enough data for the estimation of odds ratio (OR) or relative risk (RR).

Studies were excluded if any of the following parameters were missing: enough data for the estimation of OR or RR; treatment outcomes; control interventions; UDCA+GC intervention; or evaluation of the treatment outcomes. In addition, animal experiments or studies of BA etiology and pathogenesis were excluded.

2.3. Search method for identification of studies

The following databases were searched for relevant studies published up to May 2017, in either English or Chinese languages: Medline, PubMed, Cochrane, EMBASE, CNKI, CBM-disc, and VIP. The MeSH terms included “BA,” “bile ducts,” “hepatopancreatobiliary,” and “Kasai procedure.” The search criteria were further extended by using the following additional MeSH terms: “steroids,” “corticosteroids,” “dexamethasone,” “methylprednisolone,” “hydrocortisone,” “ursodeoxycholic acid,” “ursodiol,” “ursodeoxycholic acid,” “3 alpha, 7 beta-dihydroxy-5 beta-cholan-24-oic acid,” “urso,” “deoxyursodeoxycholic acid,” and “cholestyramine.” Retrieval of all relevant studies was based on consensus between all authors, and in addition, the reference list of the selected articles was further searched for additional relevant studies.

2.4. Data collection and extraction

Cochrane Handbook for Systematic Reviews of Interventions, version 5.3.5, guidelines were followed to undertake this meta-analysis. The methodological quality of the selected studies was assessed by 2 authors, independently, following Newcastle–Ottawa Scale for assessment of the quality of non-randomized studies in meta-analyses. Based on it, information about the following data points was extracted: GC type, dose, timing of its administration, and duration of the therapy. Bias risk trials were marked as “A” (low) with a score of 7 to 9, “B” (medium) with a score of 4 to 6, or “C” (high) with a score of 1 to 3. The Jadad scoring standard was applied for RCTs.

Two authors independently evaluated newly identified trials, based on the inclusion criteria, and extracted the data. Any disagreements were resolved by discussion with a 3rd author.

2.5. Data analysis

The meta-analysis was performed using Review Manager 5.2 software. Heterogeneity was explored by $I^2$ test with significance set at $P < .1$, and heterogeneity was measured using the $I^2$ statistic before the meta-analysis. Heterogeneity judged as $I^2 < 25\%$ was considered good, while $I^2$ of 25% to 50% was reasonable. However, an $I^2$ value > 50% signaled significant heterogeneity, and on this basis, it was decided not to statistically combine their results.

The pooled ORs and 95% confidence intervals (CIs) were calculated based on random-effects model, due to the more conservative approach of this particular model. As there are few studies of BA, it was assumed that an OR from a case-control study can be approximated as a risk ratio in a cohort study. Due to the lack of significant heterogeneity, cohort studies were statistically combined with case-control studies for meta-analysis.

3. Results

3.1. Characteristics of included studies

The extensive electronic database search yielded 460 studies, and an additional 5 studies were identified through hand search (Fig. 1). After exclusion of duplicate and irrelevant studies, 8 studies that were described as observational (involving 530 patients), were included in this meta-analysis (Table 1). The 144 patients in case-control studies, 152 in cohort studies, and 234 patients in RCT studies met the inclusion criteria and had sufficient data for meta-analysis. In total, 312 patients were treated with UDCA+GC, while 218 patients were treated with other therapeutic methods. The included studies were published in different countries.

The average age of the patients in each of the 8 studies was less than 90 days (Table 1). The preoperative serum bilirubin levels were similar in the UDCA+GC and control groups of 6 studies (Table 2). However, the remaining 2 studies lacked this information. The overall serum bilirubin levels were different in studies from different countries. The postoperative adjuvant therapy regimens for all patients varied among these studies (Table 3), and included intravenous antibiotics injection, prescription of fat-soluble vitamins, replacement of fat-soluble and high-caloric formula with medium-chain triglyceride oil, and oral administration of phenobarbital (phenobarb). The follow-up duration of patients after the operation varied between 1 month and 12 years, with most of them followed for 6 months (Table 5).

3.2. Quality assessment of identified trials

Newcastle–Ottawa Scale was used to assess the methodological quality of the selected studies. All trials were observed to be having a low bias and ranked as grade A, except the trial by Meyers et al. which displayed medium bias risk and ranked as grade B (Table 4).

3.3. Effect of UDCA+GC on serum bilirubin

The meta-analysis of the 8 selected studies using a random effects model revealed that despite reasonable heterogeneity, the application of UDCA and GC was superior to the control
Figure 1. Flowchart depicting the identification and selection of relevant studies.

### Table 1
Design and demographic information of the selected studies.

| First author, year | Ctry     | Design     | Subjects, n | Age at KP, d |
|-------------------|----------|------------|-------------|--------------|
|                    |          | Total      | UDCA + GC   | CON          |
|                    |          |            | UDCA + GC   | CON          |
| Davenport[16] 2013 | UK       | RCT        | 153         | 62           | 91           | MED 50 | MED 51 |
| Escobar[15] 2006  | USA      | Cohort     | 43          | 21           | 22           | 42.7 ± 16.8 | 42.7 ± 16.8 |
| Kobayashi[11] 2005 | Japan   | CC         | 63          | 51           | 12           | MED 54 | MED 54 |
| Meyers[8] 2003    | USA      | CC         | 28          | 14           | 12           | <84    | <84    |
| Petersen[14] 2008 | Germany  | Cohort     | 49          | 20           | 29           | 63 ± 32 | 57 ± 22 |
| Stringer[7] 2007  | UK       | Cohort     | 60          | 50           | 10           | MED 51 | MED 50 |
| Vejchapipat[13] 2007 | Thailand | CC         | 53          | 33           | 20           | 84.7 ± 25.7 | 98.3 ± 38 |
| Yue Ming[17] 2016 | China    | RCT        | 81          | 61           | 20           | MED 68 | MED 68 |

CC = case-control, CON = control group, Ctry = country, GC = glucocorticoid, KP = Kasai portoenterostomy, MED = median, RCT = randomized controlled trial, UDCA = ursodeoxycholic acid, UK = United Kingdom, USA = United States.
intervention in accelerating jaundice clearance (OR 2.41; 95% CI 1.44–4.04; \( P = .14 \); \( I^2 = 36\% \); Fig. 2). The overall combined effect size of these 8 studies was \( Z = 3.34, P = .0008 \), and indicated a significant difference. Funnel plot analysis was performed to reveal publication bias (Fig. 4).

### Table 2
Baseline serum bilirubin levels in the included studies.

| First author, year | UDCA + GC | CON |
|--------------------|-----------|-----|
| Davenport, 2013    | 142 ± 155 | 155 |
| Escobar, 2006      | 138.5 ± 66.7 | 138.5 ± 66.7 |
| Kobayashi, 2005    | NA        | NA  |
| Meyers, 2003       | 153.9     | 136.5 |
| Petersen, 2008     | 175 ± 67  | 165 ± 60 |
| Stringer, 2007     | NA        | NA  |
| Vejjchapipat, 2007 | 189.8 ± 44.5 | 176.13 ± 49.6 |
| Yue, 2016          | 78.51 ± 20.13 | 75.33 ± 25.48 |

SBL = serum bilirubin level, UDCA = ursodeoxycholic acid.

### Table 3
Treatment regimens of the included studies.

| First author, year | Regimen | GC | Adjuncts |
|--------------------|---------|----|----------|
| Davenport, 2013    | Low: oral PND 2 mg/kg/d for 2 wk from D7 postop, then 1 mg/kg/d D22-228 | 1/2 sachet bid | MCT, antibiotics, phenobarb |
| Escobar, 2006      | Most use is IV PND & Dex from 20 mg/kg/d to 2 mg/kg/d tapers lasting 2–4 wk | No dose mentioned | Antibiotics, phenobarb, fat-soluble vitamin |
| Kobayashi, 2005    | Oral prednisolone: Group 1, no prednisolone; Group 2, taper to 6, 4, 2 mg; Group 3, taper to 10, 5, 2.5 mg; Group 4, taper to 20, 15, 10, 5, and 2.5 mg; Group 5, as in Group 4, protocol restarted if necessary | No dose mentioned | Phenobarb, taurine |
| Meyers, 2003       | IV MP 10 mg/kg at KP; taper over 7 d to 2 mg/kg/d; then prednisone 2 mg/kg/d × 8–12 wk | 20 mg/kg/d | Antibiotics |
| Petersen, 2008     | IV MP 10 mg/kg D1–5; 0.1 mg/kg D6–28 | 25 mg/kg/d | Antibiotics, MCT, fat-soluble vitamins |
| Stringer, 2007     | Oral dexamethasone: 0.3 mg/kg bid for 5 d; 0.2 mg/kg bid for 5 d; 0.1 mg/kg bid for 5 d; 0.07 mg/kg bid for 5 d; beginning on postop D5 | 5 mg/kg bid | Phenobarb, ranitidine, antibiotics |
| Vejjchapipat, 2007 | Oral prednisolone: 4 mg/kg/d D7; post-KP × 3–4 d; then every 2 d × 4–12 wk depending on jaundice status | 10–15 mg/kg/d | Antibiotics, fat-soluble vitamins |
| Yue, 2016          | IV MP 4 mg/kg/d from D3; taper (every 3 d) to 4 mg/d × (18–24) wk | No dose mentioned | Antibiotics, calcium, vitamin |

Bid, twice/day, GC = glucocorticoid, IV = intravenous, KP = Kasai portoenterostomy, MCT = medium chain triglyceride formula, MP = methylprednisolone, UDCA = ursodeoxycholic acid.

### Table 4
Assessment of risk bias in the selected studies by study design.

| First authors | Year | Country | Selection | Comparability | Exposure | GS |
|---------------|------|---------|-----------|---------------|----------|----|
| CC            | Meyers 2003 | USA | *** | — | ** | 5 |
| Kobayashi 2005 | Japan | **** | ** | ** | 8 |
| Vejjchapipat 2007 | Thailand | **** | ** | ** | 7 |
| Cohort       | Petersen 2008 | Germany | **** | ** | ** | 8 |
| Stringer 2007 | UK | **** | ** | ** | 9 |
| Escobar 2006 | USA | **** | ** | ** | 8 |
| RCT          | Davenport 2013 | UK | **** | ** | ** | 8 |
| Yue 2016     | China | **** | ** | ** | 7 |

Grade A, low bias risk (7–9 points); Grade B, moderate bias risk (4–6 points). Each asterisk (*) represents one point.

CC = case-control, QS = quality score, RCT = randomized controlled trial, UK = United Kingdom, USA = United States.

### Table 5
Postoperative features of the included studies.

| First author, year | UDCA + GC | CON |
|--------------------|-----------|-----|
| Davenport, 2013    | 49, FU 6 mo | 39, FU 6 mo |
| Escobar, 2006      | 16, FU 6 mo | 8, FU 6 mo |
| Kobayashi 2005     | 39, difference | 7, difference |
| Petersen 2008      | 10, mean FU 3.8 y | 1, mean FU was 3.8 y |
| Stringer 2007      | 11, 6 mo post-KPE; 6, 2 y post-KPE | 20, 6 mo post-KPE; 6, 2 y post-KPE |
| Vejjchapipat 2007  | 3.3 MED, FU 0.1–12 y | 4.4 MED, FU 1.8–5.2 y |
| Yue 2016          | 20, FU 6 mo | 10, FU 6 mo |
| Yue 2016          | 38, FU 6 mo | 8, FU 6 mo |

CON = control group, FU = follow-up, KPE = Kasai portoenterostomy, MED = median, UDCA = ursodeoxycholic acid.

3.4. Effect of UDCA+GC on cholangitis

A similar analysis for cholangitis showed very low heterogeneity in the 7 included studies. However, no significant advantage was observed for the UDCA+GC treatment relative to the
control (OR 0.87; 95% CI 0.43–1.74; \( P = 0.24 \); \( I^2 = 25\% \); Fig. 3), and the overall effect size was \( Z = 0.40, P = 0.69 \), with no significant difference. It is important to note that having no statistical significance does not mean that there is no efficacy at all. Rather, more studies might be required to confirm and evaluate the effectiveness of UDCA+GC on cholangitis. In addition, a funnel plot was created to reveal publication bias (Fig. 5).

4. Discussion

Our meta-analysis, based on 8 studies including 530 patients with BA younger than an average 90 days, showed that after Kasai portoenterostomy, adjuvant steroid therapy in combination with UDCA may significantly improve postoperative clearance of jaundice. However, this may not favorably affect the incidence rate of cholangitis in these patients.

Several retrospective studies have also shown that high-dose steroids has the potential to improve the clinical outcomes of BA after surgery.[15,18,19] Specifically, the studies by Vejchapipat et al,[13] Meyer et al,[8] and Kobayashi et al[11] reported no specific complications due to steroid treatment except fluid retention and increased appetite. But, in this group, surgical complications including 1 wound infection and 1 gut obstruction from adhesion band were observed, and treated with another operation. Similarly, the complications in the non-steroid group also included 1 child with wound infection and 2 children with gut obstruction, but were treated by non-operative methods.

One infant in the study by Stringer et al.[12] had gastrointestinal bleeding, which could be due to dexamethasone, but later it was treated with ranitidine treatment. This study also reported that 39 (70%) of the 50 children who received GC were alive with their native liver, with median follow-up of 3.3 years, and 17 others who received successful liver transplantation (LT) were alive and healthy. Meyer et al[10] reported that fewer patients required LT in the steroid group (21%) compared with the control group (85%) or died during the 1st year of life (\( P < 0.01 \)). Petersen et al[14] in their study did not report any GC-related complications, and observed that patients with native liver had 63% overall survival after 6 months, and 31% after 2 years. However, no statistical difference was noted between the GC and control groups. Similarly, the study by Vejchapipat et al[13] also suggested that use of steroids appeared helpful, but did not significantly improve early outcome in BA patients. In contrast, 2 systematic reviews conducted by Sarkhy et al[20] and Zhang et al[21] indicated that postoperative steroid treatment was not superior to standard treatment. In addition, Petersen et al[14] demonstrated that after Kasai procedure, high-dose steroid pulses were not very effective in postoperative adjuvant therapy protocols.

UDCA, a hydrophilic bile acid, constitutes only 1% to 4% of the total bile acid in humans.[22] The study by Willot et al[23] evaluated the effects of UDCA on liver function of 16 children with BA and showed that its beneficial effects persist for several years after the Kasai procedure. Thus, this study supported the use of prolonged UDCA treatment for children with successful surgery for BA. The potential mechanism of UDCA may be via immunomodulatory properties that can result in clearing of toxic endogenous bile acids. It confers a cytoprotective effect on hepatocytes, and decreases the proliferation of mononuclear cells.
Figure 4. Funnel plot analysis to assess the publication bias in the studies showing the effects of UDCA + GCS in normalize serum bilirubin levels. UDCA = ursodeoxycholic acid.

Figure 5. Funnel plot analysis to assess the publication bias in the studies showing the effects of UDCA + GCS on cholangitis. UDCA = ursodeoxycholic acid.
and cytokine production. The study by Yamashiro et al. showed that increasing the serum concentration of UDCA could decrease toxic endogenous bile salts, thereby highlighting the protective function of UDCA in hepatocytes and cholangiocytes. Therefore, this study provided additional support for the potential benefit of UDCA in BA.

UDCA has been shown to suppress the inflammatory response, which is a key factor in the pathogenesis of some cases of BA. According to the study by Ou et al. (2006), the expression of interleukin bile acid transporters was enhanced by GC, and resulted in increased enterohepatic recirculation along with suppression of actual bile acid synthesis, due to inhibition of rate-controlling enzymes. Importantly, in our meta-analysis, the effects of UDCA + GC on postoperative outcomes of the Kasai surgery in BA patients were evaluated relative to placebo or other intervention. The random effects model revealed that application of combined UDCA and GC is superior to control interventions in accelerating the clearance of serum bilirubin. However, in 5 studies, the CI crossed the neutral line, thus indicating that there was no difference between the groups.

It is important to note that this meta-analysis is clearly limited by the small number of trials available for analysis. Secondly, heterogeneity was analyzed irrespective of the blood levels of the medicine in the analyzed patients. The methodological quality of some of the included trials was only moderate, as they were not double-blinded, and the methods of randomization were not described explicitly. This may have led to exaggerated estimates of interventional benefits or contributed to discrepancies in the results. The observational nature of the included studies makes them prone to selection and performance bias. Although we tried to minimize these effects by restricting the eligibility criteria, the influence of confounding factors cannot be ignored or eliminated. For example, in most of these studies, patients were assigned to the UDCA + GC or placebo groups based on the preference of the individual health care provider, and no other predetermined criteria. It is unclear from these studies whether a positive outcome was the result of selection bias, performance bias, or the effect of UDCA + GC. In addition, experienced caregivers were more inclined to use UDCA + GC (as well as other postoperative regimens, including antibiotics or cholecystectomy) given their expertise with the surgical and postoperative management of BA. Moreover, all these articles were clinical observations and the experiences of different doctors were never the same, and this could have eventually led to different clinical outcomes. In addition, our meta-analysis only included studies published in English or Chinese, and therefore to some extent, our study is also prone to selection bias. Most importantly, there were significant discrepancies among the different studies regarding treatment protocols, including different UDCA + GC ratios and dosages, routes of administration, and duration of therapy. Each of these factors can contribute to variations in results among the studies.

In summary, our meta-analysis demonstrated that application of UDCA + GC was superior to control (placebo or other) intervention, in patients who have undergone Kasai procedure. However, due to multiple limitations as described above, and particularly due to the challenges associated with the design of each published study, we suggest cautious interpretation of our results. Specifically, our findings emphasized the difficulties associated with applying evidence-based decision making, especially with the use of UDCA + GC, and thus currently it is difficult to make any concrete recommendations regarding the use of UDCA + GC treatment in the postoperative management of BA. Hence, we stress the need for a large, randomized, prospective double-blinded study to address the effectiveness of UDCA + GC on postoperative outcomes of the Kasai procedure in the treatment of BA patients.

Acknowledgments

This study was fully supported by Nation Natural Science Foundation of China.

Author contributions

Data curation: Jian-Li Qiu, Ming-Yi Shao, Wen-Fang Xie, Yue Li, Hai-Die Yang, Min-Min Niu.
Funding acquisition: Hua Xu.
Investigation: Jian-Li Qiu, Wen-Fang Xie, Yue Li.
Methodology: Hai-Die Yang, Min-Min Niu.
Resources: Ming-Yi Shao.
Software: Ming-Yi Shao.
Supervision: Hua Xu.
Writing – original draft: Jian-Li Qiu.
Writing – review & editing: Jian-Li Qiu, Hua Xu.

References

[1] Hsiao CH, Chang MH, Chen HL, et al. Universal screening for biliary atresia using an infant stool color card in Taiwan. Hepatology 2008;47:1233–40.
[2] Sokol RJ, Shepherd RW, Superina R, et al. Screening and outcomes in biliary atresia: summary of a National Institutes of Health workshop. Hepatology 2007;46:566–81.
[3] Feldman AG, Mack CL. Biliary atresia: cellular dynamics and immune dysregulation. Semin Pediatr Surg 2012;21:192–200.
[4] Sermet MO, Wildhaber BE, Broué P, et al. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. Pediatrics 2009;123:1280–6.
[5] Carey EJ, Lindor KD. Current pharmacotherapy for cholestatic liver disease. Expert Opin Pharmacother 2012;13:2473–84.
[6] Koth MA. Ursodeoxycholic acid in neonatal hepatitis and infantile jaundice. Dig Dis Sci 2009;54:2231–41.
[7] Chen Y, Nah SA, Chiang L, et al. Postoperative steroid therapy for biliary atresia: systematic review and meta-analysis. J Pediatr Surg 2015;50:1590–4.
[8] Meyers RL, Book LS, O’Gorman MA, et al. High-dose steroids, ursodeoxycholic acid, and chronic intravenous antibiotics improve bile flow after Kasai procedure in infants with biliary atresia. J Pediatr Surg 2003;38:406–11.
[9] Schreiber RA, Barker CC, Roberts EA, et al. Biliary atresia: the Canadian experience. J Pediatr 2007;151:659–65.
[10] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[11] Kobayashi H, Yamataka A, Koga H, et al. Optimum prednisolone usage in patients with biliary atresia postportoenterostomy. J Pediatr Surg 2003;40:327–30.
[12] Stringer MD, Davison SM, Rajwul SR, et al. Kasai portoenterostomy: 12-year experience with a novel adjuvant therapy regimen. J Pediatr Surg 2007;42:1324–8.
[13] Vechjapin P, Passakonrunr J, Soopkataram P, et al. High-dose steroids do not improve early outcome in biliary atresia. J Pediatr Surg 2007;42:2102–5.
[14] Petersen C, Harder D, Melter M, et al. Postoperative high-dose steroids do not improve mid-term survival with native liver in biliary atresia. Am J Gastroenterol 2008;103:712–9.
[15] Escober MA, Jay CA, Brooks RM, et al. Effect of corticosteroid therapy on outcomes in biliary atresia after Kasai portoenterostomy. J Pediatr Surg 2006;41:99–103.
[16] Davenport M, Parsons C, Tizard S, et al. Steroids in biliary atresia: single surgeon, single centre, prospective study. J Hepatol 2013;59:1035–8.
[17] Yue M, Yang HY, Wang JX. The clinical strategies of hormone in the treatment of biliary atresia after Kasai procedure. Medicine & Philosophy 2016;37:56–8.
[18] Muraji T, Nio M, Ohhama Y, et al. Postoperative corticosteroid therapy for bile drainage in biliary atresia—a nationwide survey. J Pediatr Surg 2004;39:1803–5.
[19] Tatekawa Y, Muraji T, Tsugawa C. Glucocorticoid receptor alpha expression in the intrahepatic biliary epithelium and adjuvant steroid therapy in infants with biliary atresia. J Pediatr Surg 2005;40:1574–80.
[20] Sarkhy A, Schreiber RA, Milner RA, et al. Does adjuvant steroid therapy post-Kasai portoenterostomy improve outcome of biliary atresia? Systematic review and meta-analysis. Can J Gastroenterol 2011;25:440–4.
[21] Zhang D, Yang HY, Jia J, et al. Postoperative steroids after Kasai portoenterostomy for BA: a meta-analysis. Int J Surg 2014;12:1203–9.
[22] Kumar D, Tandon RK. Use of ursodeoxycholic acid in liver diseases. J Gastroenterol Hepatol 2003;16:3–14.
[23] Willot S, Uhlen S, Michaud L, et al. Effect of ursodeoxycholic acid on liver function in children after successful surgery for biliary atresia. Pediatrics 2008;122:e1236–41.
[24] Kotb MA. Molecular mechanisms of ursodeoxycholic acid toxicity & side effects: ursodeoxycholic acid freezes regeneration & induces hibernation mode. Int J Mol Sci 2012;13:8882–914.
[25] Yamashiro Y, Ohtsuka Y, Shimizu T, et al. Effects of ursodeoxycholic acid treatment on essential fatty acid deficiency in patients with biliary atresia. J Pediatr Surg 1994;29:425–8.
[26] Out C, Dikkers A, Laskewitz A, et al. Prednisolone increases enterohepatic cycling of bile acids by induction of Asbt and promotes reverse cholesterol transport. J Hepatol 2014;61:351–7.