Systematic Review and Meta-Analysis

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Effect of combined ursodeoxycholic acid and glucocorticoid on the outcome of Kasai procedure

A systematic review and meta-analysis

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Abstract

Introduction: Multiple studies have investigated the effect of ursodeoxycholic acid (UDCA) or glucocorticoid (GC) on the outcome of the hepatoportoenterostomy (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, hepatoportoenterostomy, ursodeoxycholic acid

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The authors report no conflicts of interest.

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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 malformation. Viruses under consideration include rotavirus, reovirus, and cytomegalovirus.[3]

Currently, the Kasai procedure (i.e., hepatoportoenterostomy) 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.[2,4] Survival rates are reportedly improved by administration of glucocorticoid (GC) to reduce inflammation, ursodeoxycholic acid (UDCA) to relieve jaundice,[5] 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," "hepatoportoenterostomy/portoenterostomy," and "Kasai procedure." The search criteria were further extended by using the following additional MeSH terms: "steroids," "corticosteroids," "dexamethasone," "methyl/prednisolone," "hydrocortisone," "ursodeoxycholic acid," "ursodiol," "ursodeoxycholic acid," "3 alpha, 7 beta-dihydroxy-5 beta-cholan-24-oic acid," "urso," "deoxyursocholic 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 Q 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.[10] 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[8,11–17] that were described as observational (involving 530 patients), were included in this meta-analysis (Table 1). The 144 patients in case-control studies,[8,11,13] 152 in cohort studies,[12,14,15] and 234 patients in RCT studies[16,17] 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[11,12] 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,[8] 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

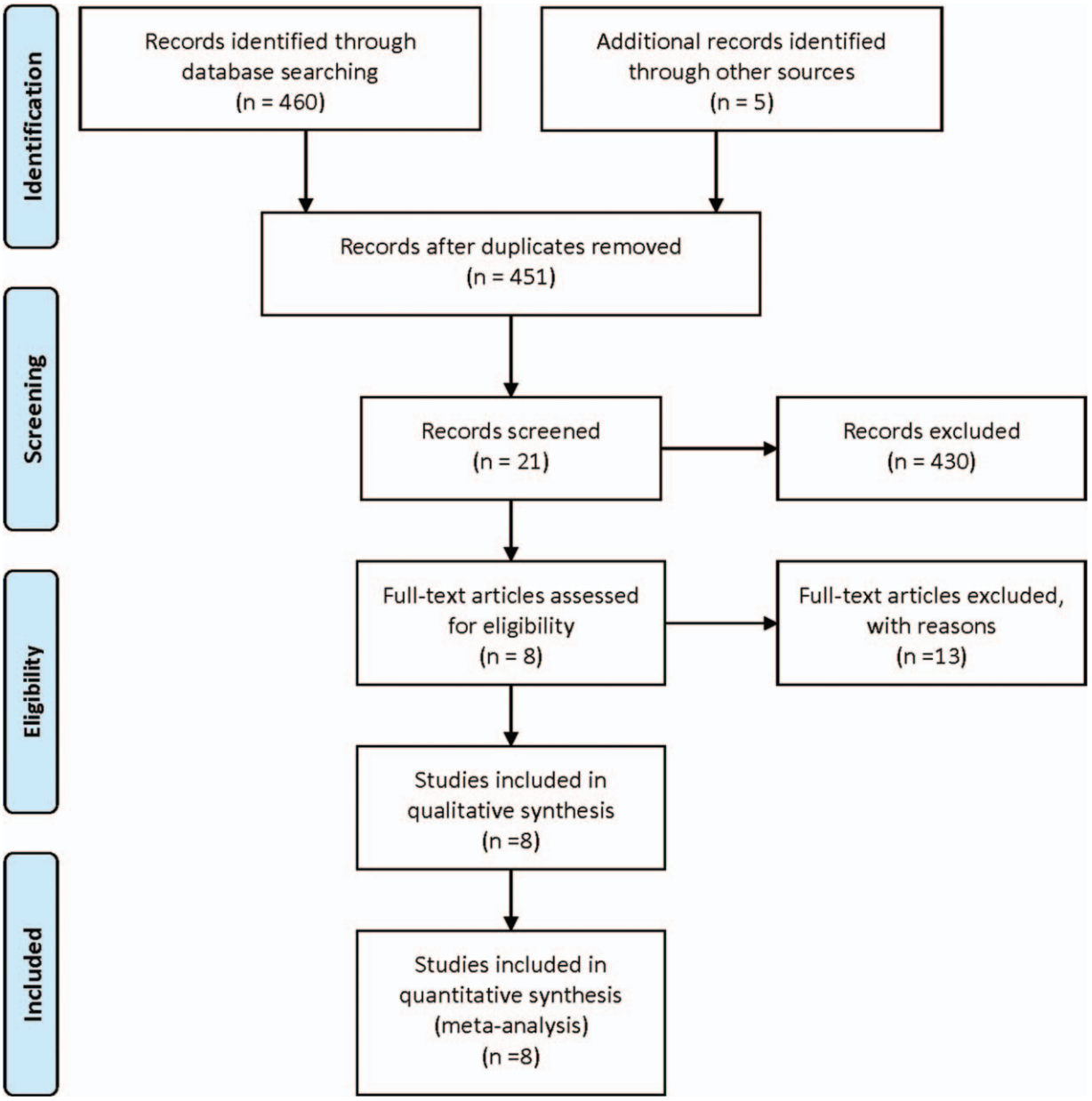

Figure 1. Flowchart depicting the identification and selection of relevant studies.

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
					1		91
					1		112
Petersen,[14] 2008	Germany	Cohort	49	20	29	63 ± 32	57 ± 22
Stringer,[12] 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.

Table 2

Baseline serum bilirubin levels in the included studies.

First author, year	SBL at KP, μmol/L	
	UDCA + GC	CON
Davenport,[16] 2013	142	155
Escobar,[15] 2006	138.5 ± 66.7	138.5 ± 66.7
Kobayashi,[11] 2005	NA	NA
Meyers,[8] 2003	153.9	136.5
Petersen,[14] 2008	175 ± 67	165 ± 60
Stringer,[12] 2007	NA	NA
Vejchapipat,[13] 2007	189.8 ± 44.5	176.13 ± 49.6
Yue,[17] 2016	78.51 ± 20.13	75.33 ± 25.48

CON = control group, GC = glucocorticoid, KP = Kasai portoenterostomy, SBL = serum bilirubin level, UDCA = ursodeoxycholic acid.

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 5

Postoperative features of the included studies.

First author, year	Postop characteristics (jaundice-free with native liver)	
	UDCA + GC	CON
Davenport,[16] 2013	49, FU 6 mo	39, FU 6 mo
Escobar,[15] 2006	16, FU 6 mo	8, FU 6 mo
Kobayashi,[11] 2005	39, difference between groups	7, difference between groups
Meyers,[8] 2003	10, mean FU 3.8 y	1, mean FU was 3.8 y
Petersen,[14] 2008	11, 6 mo post-KPE; 6, 2 y post-KPE	20, 6 mo post-KPE; 6, 2 y post-KPE
Stringer,[12] 2007	3.3 MED, FU 0.1–12 y	4.4 MED, FU 1.8–5.2 y
Vejchapipat,[13] 2007	20, FU 6 mo	10, FU 6 mo
Yue,[17] 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.[8,11–15,17] However, no significant advantage was observed for the UDCA + GC treatment relative to the

Table 3

Treatment regimens of the included studies.

First author, year	Regimen		
	GC	UDCA	Adjuvant
Davenport,[16] 2013	Low: oral PND 2 mg/kg/d for 2 wk from D7 postop, then 1 mg/kg/d D22-D28	1/2 sachet bid	MCT, antibiotics, phenobarb
Escobar,[15] 2006	Most use is IV PND & Dex from 20 mg/kg/d to 2 mg/kg/d tapers lasting 2–6 wk	No dose mentioned	Antibiotics, phenobarb, fat-soluble vitamin
Kobayashi,[11] 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,[8] 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,[14] 2008	IV MP 10 mg/kg/d D1–5; 1 mg/kg/d D6-28	25 mg/kg/d	Antibiotics, MCT, fat-soluble vitamins
Stringer,[12] 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; beginning on postop D5	5 mg/kg bid	Phenobarb, ranitidine, antibiotics
Vejchapipat,[13] 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,[17] 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	QS
CC	Meyers[8]	2003	USA	***	—	**	5
	Kobayashi[11]	2005	Japan	****	**	**	8
	Vejchapipat[13]	2007	Thailand	****	*	**	7
Cohort	Petersen[14]	2008	Germany	****	**	**	8
	Stringer[12]	2007	UK	****	**	***	9
	Escobar[15]	2006	USA	****	**	**	8
RCT	Davenport[16]	2013	UK	****	**	**	8
	Yue[17]	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.

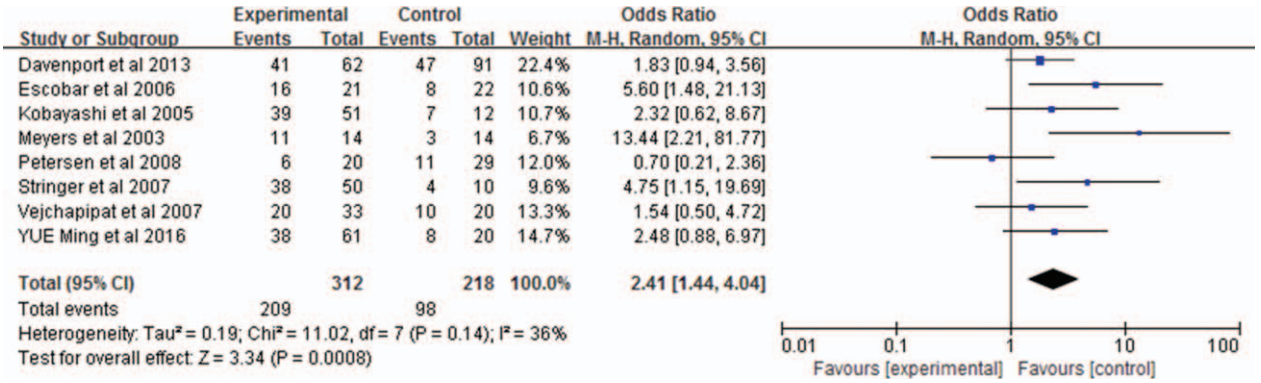

Figure 2. Meta-analysis of the effect of UDCA + GCS to normalize serum bilirubin levels. UDCA = ursodeoxycholic acid.

control (OR 0.87; 95% CI 0.43–1.74; $P = .24$; $I^2 = 25\%$; Fig. 3), and the overall effect size was $Z = 0.40$, $P = .69$, 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[8] 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 ($P < .01$). 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

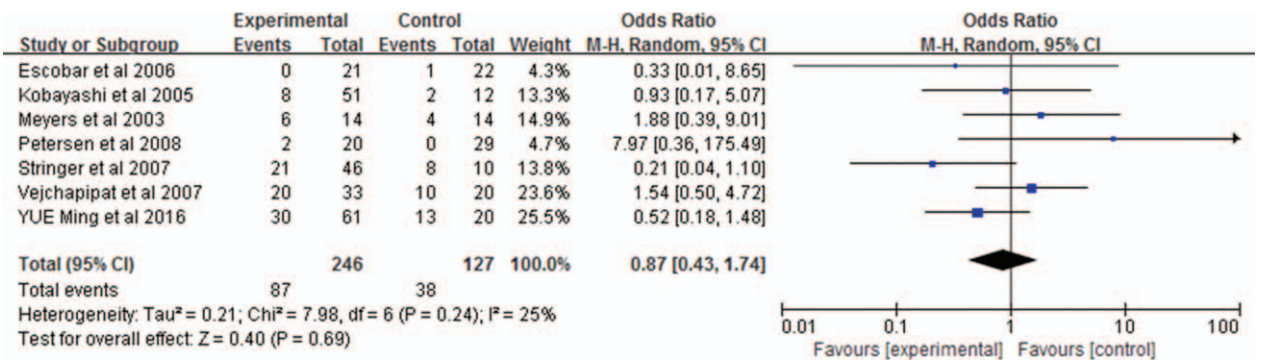

Figure 3. Meta-analysis of the effect of UDCA + GCS on cholangitis. UDCA = ursodeoxycholic acid.

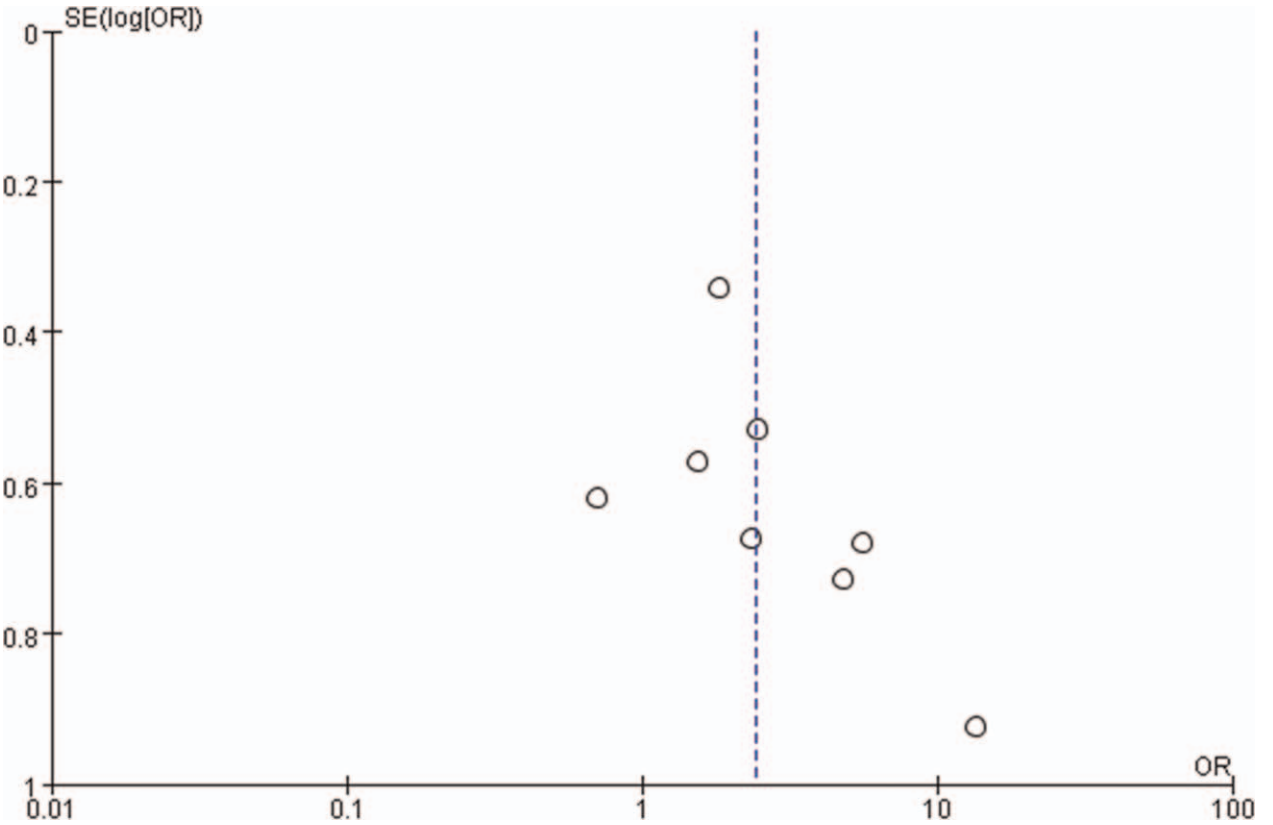

Figure 4. Funnel plot analysis to assess the publication bias in the studies showing the effects of UDCA + GCS in normalize serum bilirubin levels. UDCA = ursodeoxycholic acid.

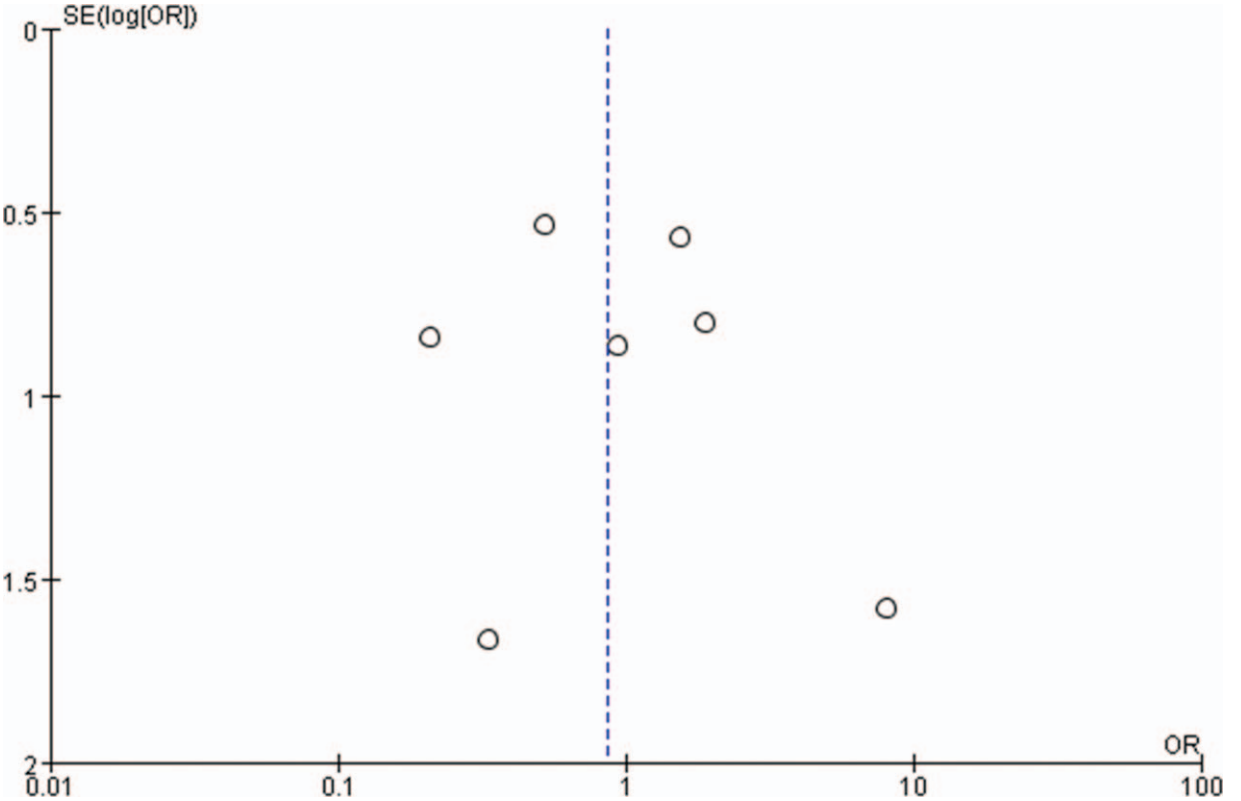

Figure 5. Funnel plot analysis to assess the publication bias in the studies showing the effects of UDCA + GCS on cholangitis. UDCA = ursodeoxycholic acid.

and cytokine production.[24] The study by Yamashiro et al[25] 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.

GC 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 Out et al,[26] the expression of ileal 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,[11,13,14,16,17] 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 choleretic agents) 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.

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Supervision: Hua Xu.
Writing – original draft: Jian-Li Qiu.
Writing – review & editing: Jian-Li Qiu, Hua Xu.

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