Efficacy, Effectiveness, and Safety of Phenobarbital in the Treatment of Cholestasis and as a Premedication to Improve Diagnostic Accuracy of Hepatobiliary Scintigraphy: A Systematic Review

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ABSTRACT

Objective. Phenobarbital is an inductor of microsomal hepatic enzyme and used as choleretic for cholestatic liver disease to enhance bile flow. It is also used as a premedication for hepatobiliary scintigraphy (HIDA) scan to improve diagnostic accuracy for an obstructive liver disease. We reviewed the available literature on the use of Phenobarbital for treatment of cholestasis and its utility as a premedication for HIDA scan.

Methods. All published studies before June 30, 2023 that investigated the efficacy, effectiveness or safety of Phenobarbital in cholestatic jaundice and its effect on the accuracy of hepatobiliary scintigraphy in diagnosis of obstructive jaundice were included. Electronic databases were searched including MEDLINE via PubMed,Cochrane Library, medRxIV, BioRxIV, as well as the following registries for ongoing and completed trials: ClinicalTrials.gov (USA); ChiCTR.org. (China); and the WHO International Clinical Trials Registry Platform. We screened abstracts, reviewed full texts, and extracted relevant information on study design, settings, population, and outcomes. There was no age and language restriction. Two reviewers independently rated the quality of included studies using: Joanna Briggs Institute critical appraisal tool for case reports, case series, and diagnostic accuracy; Newcastle – Ottawa Quality Assessment Scale for cohort studies, and Cochrane Risk of Bias for Randomized Trials. Risk of bias was appraised and GRADE certainty of evidence was judged. Pooled analysis was done using Stata 14 and reported as sensitivity and specificity.

Results. Included were nine reports on Phenobarbital as treatment for cholestasis (one case report, five case series, one cohort and two randomized studies) and seven studies (four diagnostics, two cohorts, one randomized trial) on its use as a premedication for HIDA scan. The quality of case report and case series were considered fair; cohort studies as good; and diagnostic studies were included based on overall assessment. The randomized studies had some or high risk for bias due to concerns in randomization process, measurement of outcome, and risk in the selection of reported results.

There were 31 patients (16 adults and 15 children) from case reports and case series. Of the 16 adults, serum total bilirubin concentrations declined from 4 to 70% from baseline in 13 of 15 (87%) patients after Phenobarbital was given at 120 to 250 mg per day from 22 days to five months. Eleven of 14 with pruritus at onset also had improvement in intensity of itching. Of the 15 pediatric patients, ten (67%) showed a decrease from 10 to 60% of the baseline total bilirubin but not a normalization with Phenobarbital intake at a dose of 3 to 12 mg/kg/day

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from one to 21 months. Five of 14 children also had relief of itching after treatment.

Phenobarbital compared to Ursodeoxycholic acid had limited efficacy in reducing the bilirubin levels in neonates and young infants with cholestasis.

Moderate certainty evidence showed that with Phenobarbital pretreatment, the hepatobiliary scan done on patients with neonatal cholestasis had 100% (CI 99.2, 100; I^2 = 0.0%) sensitivity and 80.2% (CI 65.4, 92.1; I^2 = 76.6%) specificity while no Phenobarbital pretreatment had 100% (94.9, 100; I^2 = 0.0%) sensitivity and 89.5% (CI 77.0, 98.1; I^2 = 11.4%) specificity. Adverse effects of Phenobarbital were drowsiness, lethargy, poor feeding, and irritability.

Conclusion. There was limited effectiveness of Phenobarbital in decreasing bilirubin levels in cholestatic liver disease. Moderate certainty evidence demonstrated that premedication with Phenobarbital did not improve the specificity of HIDA scan in the diagnosis of obstructive jaundice of infancy. Neurologic symptoms were observed with Phenobarbital intake.

Keywords: phenobarbital, cholestasis, scintigraphy, pruritus

INTRODUCTION

Cholestasis is the impairment of bile flow and is always considered pathologic as it indicates hepatobiliary dysfunction. It is defined as conjugated bilirubin more than 1 mg/dL [17.1 μmol/L; when the total bilirubin is <5 mg/dL (85.5 μmol/L)] or more than 20% of the total bilirubin [when the total bilirubin is >5 mg/dL (85.5 μmol/L)].[1] It is important to identify the cause of the cholestasis for optimal treatment and prognosis. In our institution, sixty percent of infantile cholestatic jaundice in the first three months of life had a clinical and histologic diagnosis of idiopathic neonatal hepatitis while the rest were biliary atresia (37%) and Alagille syndrome (3%).[2] Patients with biliary atresia necessitate urgent surgical intervention while those with neonatal hepatitis require medical treatment with choleretics to improve bile flow and prevent sequelae, like malnutrition due to malabsorption of fat and fat soluble vitamins. Cholestatic liver disease associated with total parenteral nutrition (TPN) has also been a recognized clinical problem in the neonates.[3]

Phenobarbital is an inductor of microsomal liver enzyme and used as a choleretic by increasing the bile acid synthesis and bile flow, independent of the bile salts.[4] The usual oral dose in pediatrics is 3-5 mg/kg/day,[5-9] but has been used as high as 10 mg/kg/day. Its main side effects are sedation and behavioral changes. In adults, it is from 120 to 250 mg per day.[7,10] Phenobarbital has also been used as a premedication before hepatobiliary scintigraphy (HIDA) to increase the specificity for an obstructive cause as it could enhance bilirubin conjugation and excretion of the radiotracer.[11-17] There are conflicting reports on the effectiveness of Phenobarbital as a treatment of cholestasis and in augmenting the accuracy of HIDA scan. In this systematic review, we reviewed the available literature on the efficacy, effectiveness, and safety on the use of Phenobarbital for treatment of cholestatic liver disease and its utility as a premedication for HIDA scan.

METHODS

We comprehensively searched various electronic databases that included MEDLINE via PubMed, Cochrane Library, medRxIV, BioRxIV, as well as the following registries for ongoing and completed trials: ClinicalTrials.gov (USA); ChiCTR.org. (China); and the International Clinical Trials Registry Platform (ICTRP, WHO). The last search date was June 30, 2023 using a combination of subject headings and keywords based on population, intervention, comparator, outcome (PICO): P – cholestatic patients; I – Phenobarbital; C – no treatment; and O – improvement in bilirubin levels or increased excretion in non-excreters in HIDA scan. We included all published reports or studies from September 1967 up to June 30, 2023 evaluating the efficacy, effectiveness, and safety of Phenobarbital in improving bilirubin levels among patients with cholestatic jaundice and whether Phenobarbital premedication improved the biliary excretion of patients with cholestatic jaundice on HIDA scan. We checked the reference lists of included papers and relevant systematic reviews. We also did a free search of online sources and preprint article. We screened abstracts, reviewed full texts, and extracted relevant information on study design, settings, population, and outcomes. There was no age and language restrictions. Excluded articles were those that did not meet the PICO and outside the timeframe specified. (Appendices A and B). Two reviewers independently rated the quality of included studies using the following: Joanna Briggs Institute (JBI) critical appraisal tool for case reports, case series, and diagnostic accuracy; Newcastle – Ottawa Quality Assessment Scale for analysis of cohort studies; Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Disagreement was settled by a discussion between the two reviewers. In patients with missing data, the specific variable was not included in the analysis. GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach was used to determine the certainty of evidence. For each included study, the number of true positives, false positives, true negatives, and false negatives were extracted using the metaprop statistical program Stata 14 software to determine the pooled sensitivity and specificity of the HIDA scan. Analysis was done separately for HIDA scan with or without Phenobarbital. Heterogeneity was determined using inconsistency statistics I^2 at 25%. In case of significant heterogeneity, subgroup analysis was done according to study design and duration of Phenobarbital

administration. Sensitivity analysis was done excluding studies with high risk of bias.

RESULTS

After the electronic search, there were 210 reports on Phenobarbital and cholestasis and 18 reports on Phenobarbital and hepatobiliary scan. Included were nine reports on Phenobarbital as a treatment for cholestasis (one case report,[5] five case series,[6-10] one cohort[18,19] and two randomized studies[20,21]) and seven studies (four diagnostics,[11-14] two cohorts, [15,16] one randomized trial[17]) on its use for detection of a biliary obstruction during hepatobiliary scintigraphy. (Appendices 1 and 2)

Appraisal of Studies (Appendix 3)

Phenobarbital as a Treatment of Cholestasis

The case report[10] had fair quality although it did not account the adverse effect of Phenobarbital. The case series were also assessed as fair. There was selection bias in four,[5-7,9] as there was no mention if the patients were consecutively included and if there was complete inclusion of patients over a time period; and in one, the report[8] was limited to two siblings. There was also no information of the clinic demographic site so that the reader could decide on its applicability to their setting.

There were three analytical studies, one cohort,[18] one randomized cross over trial[19], and another a randomized trial.[20] The cohort study was assessed overall to have good quality in terms of selection, comparability, and outcome. The cohorts and controls were comparable although it was not age- and sex-matched. In one study,[18] it was not stated whether an independent blind assessment of the outcome was done.

The randomized cross over trial[19] had some concerns as the randomization process and the measurement of outcome were unclear. The other trial[20] was considered high risk due to concerns in randomization process and in the measurement and selection of the outcome reported.

Phenobarbital as a Premedication for Hepatobiliary Scintigraphy

The four diagnostic studies[11-14] were acceptable in terms of directness and validity and results were considered important but three[12-14] of them were considered high risk as not all patients received the same reference standard. One study was done in Iran[12] and the others[11,13,14] in USA but the results are considered applicable for any cholestatic infant, regardless of race. Similarly, the two cohort studies[15,16] were assessed to have a good quality. The randomized study[17] was considered high risk due to concerns in randomization process, measurement of outcome, and risk in the selection of the reported result.

Result of Included Studies (Appendix 4)

Effectiveness of Phenobarbital in Treatment of Cholestasis

Case Reports/Case Series. A case report and five case series had a total of 31 cases with various liver disorders who were prescribed with Phenobarbital. Fifteen patients[5-9] were in the pediatric age group [Median (range) age: 2.5 (0.16-12) years] with diagnoses of intrahepatic biliary atresia/hypoplasia (10), progressive intrahepatic cholestasis (2), and one of each of extrahepatic biliary atresia, sclerosing cholangitis, and arteriohepatic dysplasia. The youngest patient was one month old with intrahepatic biliary atresia[5] and the oldest was 12 years with sclerosing cholangitis[7]. Of the 15 pediatric patients, ten (67%) showed a decrease from 10 to 60% of the baseline total bilirubin but not a normalization while five had no improvement when Phenobarbital was started at a dose of 3 to 12 mg/kg/day. Phenobarbital was administered from one to 21 months. Of 14 patients, with pruritus, five had relief of itching, six had a decreased in severity, and three had no improvement. Another report[9] demonstrated a deterioration in the liver enzymes (ALT and AST) in four patients with obstructive cholangiopathy.

There were 16 adults [Mean (SD) age: 46 (12.4) years] most of whom had primary biliary cirrhosis (10) and the others with cholestatic hepatitis (3) and one each with sclerosing cholangitis, intrahepatic duct hypoplasia, and post-necrotic cirrhosis.[7,10] Of this, a 58-year-old female with primary biliary cirrhosis had normal bilirubin and no pruritus.[10] Serum total bilirubin concentrations declined from 4 to 70% from baseline but did not normalize in 13 of 15 (87%) patients after Phenobarbital at a dose of 120 to 250 mg per day from 22 days to five months. Eleven of 14 patients with pruritus at onset had improvement in intensity of itching. Side effect reported on the use of Phenobarbital was drowsiness.[10]

Analytical Studies. There were three studies[18-20] (one cohort, one cross randomized clinical trial, one randomly assigned trial) done to determine the efficacy of Phenobarbital in cholestasis. Two studies[18,19] compared the use of Phenobarbital and Ursodeoxycholic acid (UDCA) among infants with cholestasis. A cross over randomized clinical trial,[19] showed that Phenobarbital had no effect in reducing the direct bilirubin levels (Initial: 5.43 ± 2.63 vs Final: 6.07 ± 3.7) while UDCA reduced bilirubin levels by 2.3 mg% (Initial: 6.65 ± 3.28 vs Final: 4.36 ± 1.13, $p<0.01$). Similarly, in a retrospective cohort,[18] it was shown that UDCA (-3.96±0.28) was significantly more effective in reducing direct bilirubin than Phenobarbital (-67.73 μmol/L vs 4.79, $p<0.01$). In another study [20], of 80 patients with biliary atresia who underwent a drainage operation, Phenobarbital as compared with controls was not effective in decreasing the duration or severity of cholestasis among post operative patients, regardless of whether the drainage operation was successful or not.

Phenobarbital as a Premedication for Hepatobiliary Scintigraphy

There were seven reports[11-17] that evaluated the use of Phenobarbital before hepatobiliary scan among subjects with neonatal cholestasis to differentiate an obstructive and non-obstructive cause. Reference standard for diagnosis of obstruction from non obstruction included liver biopsy, intraoperative cholangiogram, autopsy reports or in cases of neonatal hepatitis, a combination of the clinical results, and the findings of serologic and etiologic investigations.

Four diagnostic studies[11-14] and two cohorts[15, 16] included 432 infants with neonatal cholestasis with 139 infants with biliary atresia and 293 with neonatal hepatitis syndrome. Three hundred fifty-three were treated with Phenobarbital at 5 m/kg/day from two to 28 days and 79 were not given the medication before the HIDA scan. Pooled result showed that with pretreatment with Phenobarbital, the hepatobiliary scan has a sensitivity of 100% (CI 99.2, 100) and specificity of 80.2% (CI 65.4, 92.1) (Figure 1). There was significant heterogeneity for the pooled specificity (I^2 = 76.6%) (Figure 2). Subgroup analysis by study design showed specificity of 69.2% (CI 56.5, 80.5) for the cohort studies, and 84.4% (CI 65.1, 97.5) for the diagnostic studies(Figure 2). Subgroup analysis by duration of phenobarbital administration showed specificity of 76.2 (CI 53.1, 93.8) for studies where the drug was given for 5 days, and specificity of 84.5 (CI 55.8, 100.0) for studies where there was variable duration (Figure 3). Sensitivity analysis excluding studies of high risk of bias showed specificity of 78.7 (CI 60.8, 92.5). (Figure 4). No Phenobarbital pretreatment has a sensitivity of 100% (CI 94.9, 100) and specificity of 89.5% (CI 77.0, 98.1). (Figure 5). Certainty of evidence was considered moderate on

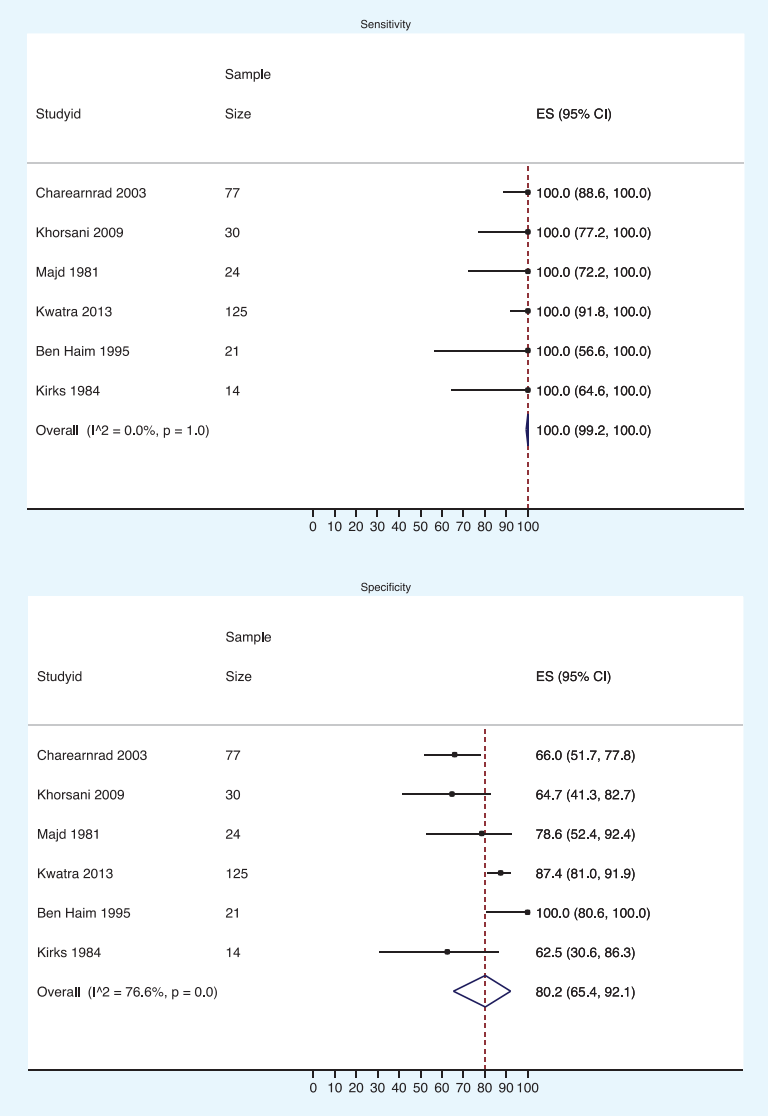

Figure 1. Forest plot on HIDA scan with phenobarbital premedication to diagnose obstruction of bile ducts in cholestatic infants.

HIDA scan with or without Phenobarbital pretreatment to diagnose obstructive jaundice in infancy. (Tables 1 and 2). As there were limited studies, no funnel plot was generated.

Similarly, a prospective cohort study with high risk of bias[17] randomly assigned 50 non-excreters with neonatal cholestasis in hepatobiliary scan to either Phenobarbital (n=20), UDCA (n=20) or normal saline (n=10). It had a high risk of bias due to concerns in randomization process, in measurement of outcome, and selection of the outcome reported. Result showed that only two patients who were given Phenobarbital, one with UDCA and one given normal saline showed excretion, thus, Phenobarbital or UDCA

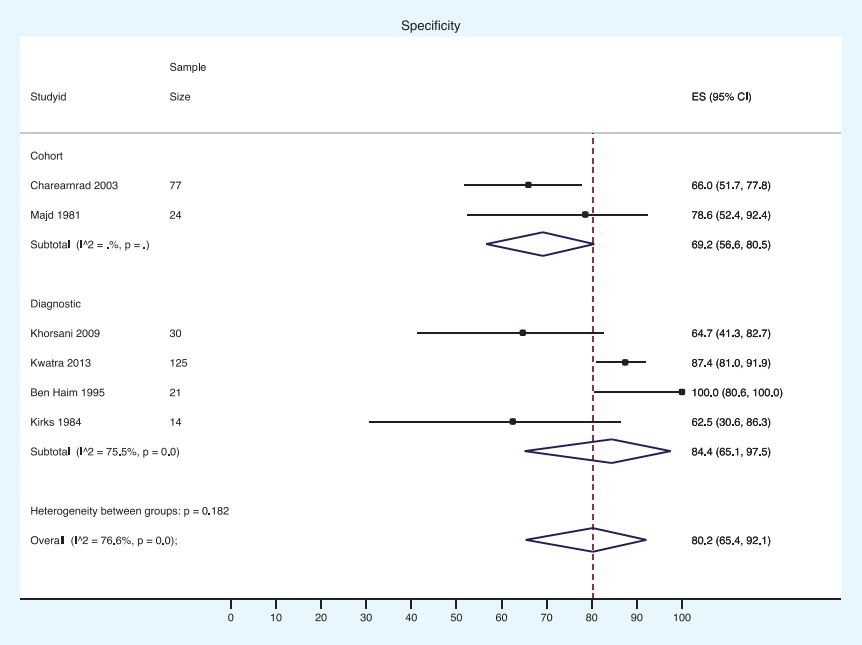

Figure 2. Forest plot on HIDA scan with phenobarbital premedication to diagnose obstruction of bile ducts in cholestatic infants (subgroup analysis by study design).

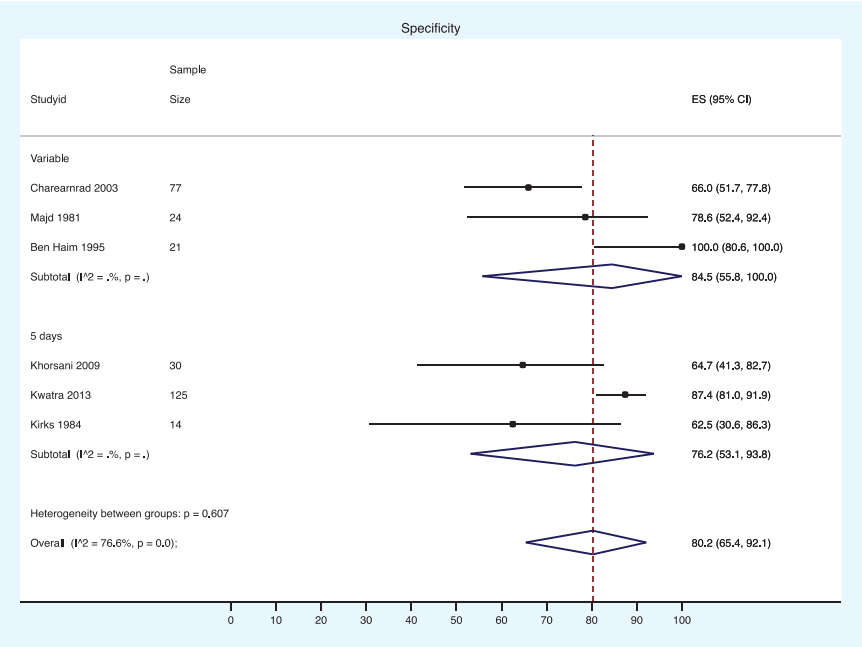

Figure 3. Forest plot on HIDA scan with phenobarbital premedication to diagnose obstruction of bile ducts in cholestatic infants (subgroup analysis by duration of phenobarbital administration).

augmented hepatobiliary scan did not improve the negative predictive value in ruling out an obstruction.

Side Effects of Phenobarbital. Side effects of Phenobarbital involved the nervous system as reported in two studies[10,12] with 34 patients. In one of the case series,[10] all four adults with cirrhosis developed drowsiness which improved by reducing the dose of the drug. Similarly, all 30 infants who had hepatobiliary scan to determine etiology of neonatal cholestasis developed lethargy, poor feeding, irritability, and hypotonia which resolved with discontinuation of the drug.[12] There were also two out of 80 infants with obstructive cholangiopathy who acquired rickets while on Pheno-

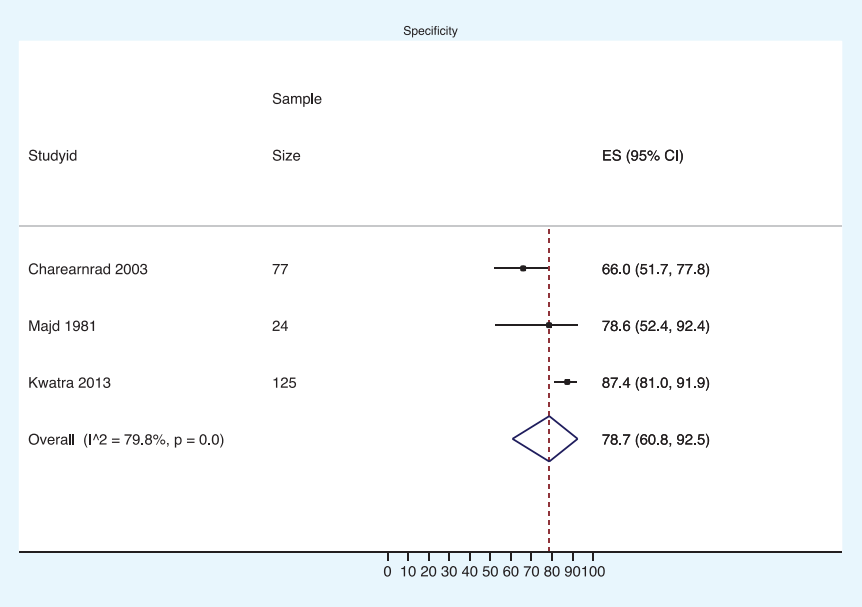

Figure 4. Forest plot on HIDA scan with phenobarbital premedication to diagnose obstruction of bile ducts in cholestatic infants (sensitivity analysis of studies with low risk of bias).

Table 1. GRADE Evidence Profile. HIDA Scan with Phenobarbital Premedication to Diagnose Obstruction of Bile Ducts in Cholestatic Infants

Sensitivity	1.00 (95% CI: 0.99 to 1.00)
Specificity	0.80 (95% CI: 0.65 to 0.92)
Prevalences	1%

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 1%	
True positives (patients with obstruction of bile ducts)	6 studies 108 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none[b]	10 (10 to 10)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having obstruction of bile ducts)								0 (0 to 0)	
True negatives (patients without obstruction of bile ducts)	6 studies 245 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none[b]	792 (644 to 911)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having obstruction of bile ducts)								198 (79 to 346)	

Explanations:
[a] *In some studies, there were issues of selection of subjects and no sample size justification.*
[b] *Publication bias is not excluded but not considered sufficient to downgrade the quality of evidence.*

barbital despite parenteral dose of Vitamin D[20] although it is unknown whether this is related to the intake of the drug.

DISCUSSION

Earlier case report[10] and case series had shown that Phenobarbital improved the degree of cholestasis in various liver disorders as reported in ten (67%) of 15 children and in 11 (73%) of 15 adults. Measures of cholestasis in these reports included reduction of serum bilirubin and bile acid levels, and enhanced hepatic clearance of bromsulphthalein and I-rose Bengal, which are organic anions that are cleared from plasma from the liver and excreted into the bile. However, these case series did not mention whether the patients were consecutively recruited over a time period thus, selection bias might have been present. While the initial reports were encouraging, a very low certainty evidence showed that Phenobarbital is not effective in the prevention of TPN-associated cholestasis in infants <1.5 kg (Table 3).[21] Neither is it effective in biliary atresia infants who underwent portoenterostomy operation,[20] regardless of whether the operation was successful or not. Furthermore, a cross over randomized controlled trial[19] and a retrospective cohort[18] showed that UDCA, a choleretic drug, was more effective than

Table 2. GRADE Evidence Profile. HIDA Scan with No Phenobarbital Premedication to Diagnose Obstruction of Bile Ducts in Cholestatic Infants

Sensitivity	1.00 (95% CI: 0.95 to 1.00)
Specificity	0.89 (95% CI: 0.77 to 0.98)
Prevalences	1%

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 1%	
True positives (patients with obstruction of bile ducts)	4 studies 31 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none[b]	10 (10 to 10)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having obstruction of bile ducts)								0 (0 to 0)	
True negatives (patients without obstruction of bile ducts)	4 studies 48 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none[b]	881 (762 to 970)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having obstruction of bile ducts)								109 (20 to 228)	

Explanations:
[a] In some studies, there were issues of selection of subjects and no sample size justification.
[b] Publication bias is not excluded but not considered sufficient to downgrade the quality of evidence.

Table 3. GRADE Evidence Profile: Phenobarbital Compared to No Treatment in Preventing Total Parenteral Nutrition-Associated Cholestasis

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Indirectness	Inconsistency	Inconsistency	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With No treatment	With Phenobarbital		Risk with No treatment	Risk difference with Phenobarbital
Occurrence of Cholestasis (follow-up: mean 85 days; assessed with: Total Bilirubin >3 mg/dL)											
31 (1 non-randomised study)	serious[a]	not serious	not serious	serious[b]	dose response gradient	⊕◯◯◯ VERY LOW	7/21 (33.3%)	6/10 (60.0%)	not estimable	7/21 (33.3%)	

CI: confidence interval

Explanations
[a] Possible selection bias as data based on retrospective review of medical charts and selection of subjects are based on the outcome.
[b] Wide confidence interval; small sample size

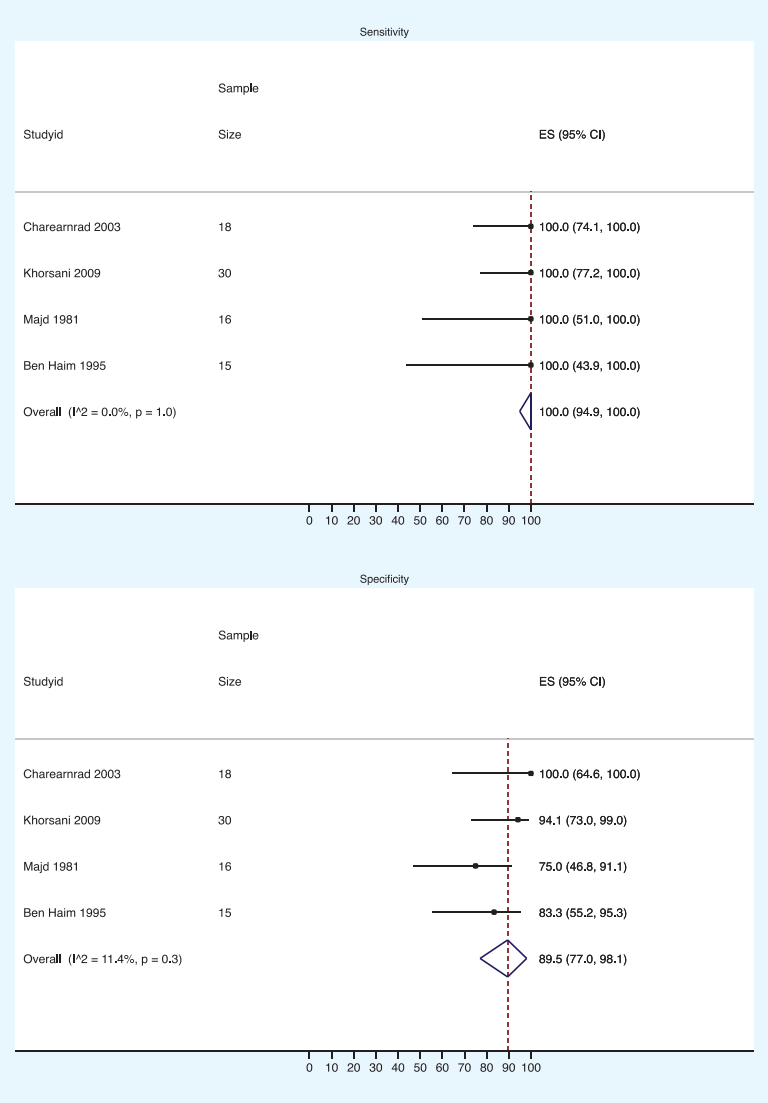

Figure 5. Forest plot on HIDA scan with no phenobarbital premedication to diagnose obstruction of bile ducts in cholestatic infants.

Phenobarbital in the treatment of infants with cholestasis. This finding is supported by a meta-analysis of 29 studies that showed that UDCA could decrease total bilirubin in children [MD= -25.67 μmol/L, 95% CI (-31.82, -19.52, P<0.000001)] with various causes of cholestatic liver disease.[22]

This review also addressed the question whether Phenobarbital premedication improves diagnostic accuracy before radionuclide studies of the hepatobiliary system. This includes the use of ^{99m}Tc-diisopropyl iminodiacetic acid (^{99m}Tc-DISIDA) or the ^{99m}Tc-methylbromo iminodiacetic acid (^{99m}Tc-mebrofenin). These compounds are not conjugated but are excreted into the bile canaliculi. By administration of Phenobarbital for five days before the radionuclide studies are done, the drug will increase hepatic transport system for organic anions, which are substrates for radiolabeled diethyl iminodiacetic acid, thus the excretion of the radiopharmaceutical and visualization of the bile ducts.[23] Pooled results of our study showed that with or without pretreatment with Phenobarbital, the hepatobiliary scan has a 100% sensitivity. On the other hand, the specificity was 80% with and 89% without Phenobarbital pretreatment in the detection of an obstructive cause of neonatal cholestasis. Even with a sensitivity analyses, the specificity in those with Phenobarbital premedication was still low in those with variable intake of the drug or in low risk of bias studies. In this setting, the specificity is important as it will avoid unnecessary operation if the HIDA scan will yield a false positive result. However, in patients with severe intrahepatic cholestasis including those with Alagille syndrome, idiopathic neonatal hepatitis or parenteral nutrition-associated cholestasis, differentiation of an obstructive and non-obstructive cause maybe difficult with hepatobiliary scan, as this will decrease

the specificity of the imaging modality as seen in some of the studies.[12,14-16] The use of Phenobarbital before ^{99m}Tc-DISIDA scan also cause a delay in diagnosis and surgical therapy of biliary atresia. Thus, other medications have been tried of which Ursodeoxycholic acid pretreatment has shown an improved specificity with minimal or no side effects.[23]

The study is limited by the data available as most of the reports that used Phenobarbital in cholestasis were case reports and case series. There is no controlled trial available, and the age and underlying diseases of patients that were included in the different studies were different. There was also a difference in the dose and duration of Phenobarbital that was used. For the use of Phenobarbital as a premedication for HIDA scan, there were some studies with high risk of bias as it used different reference standards in diagnosis of patients with obstruction including liver biopsy, cholangiogram, autopsy, and clinical course. While these modes of diagnoses maybe used, this may potentially limit the validity of the study. Nonetheless, the report provides important information as there is presently no consensus on whether Phenobarbital is effective in cholestasis and whether it should be used as a premedication for HIDA scan.

CONCLUSION

This review has shown that Phenobarbital has limited efficacy in decreasing bilirubin levels in cholestatic liver disease. Moderate certainty evidence showed that Phenobarbital augmented hepatobiliary scan did not improve the specificity of the procedure in the diagnosis of obstructive jaundice of infancy. Adverse effects of Phenobarbital involved the nervous system.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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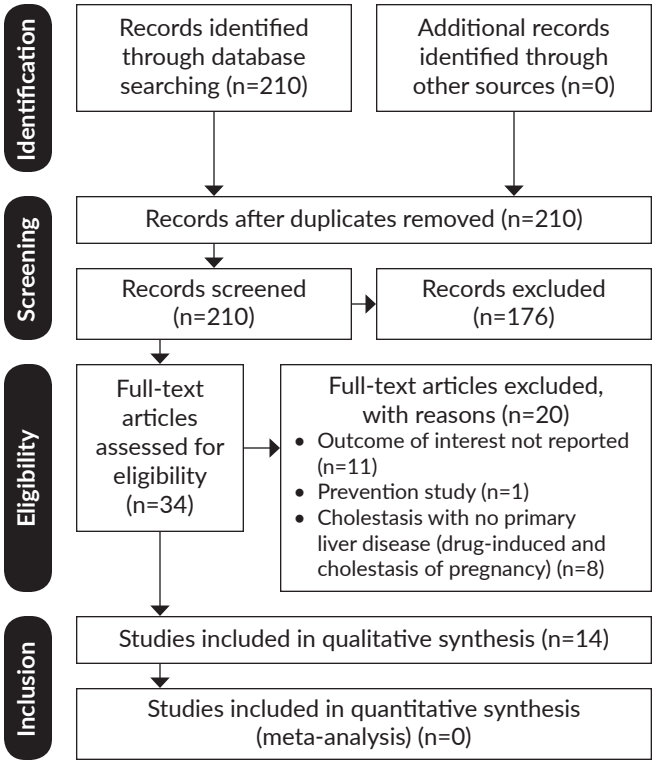
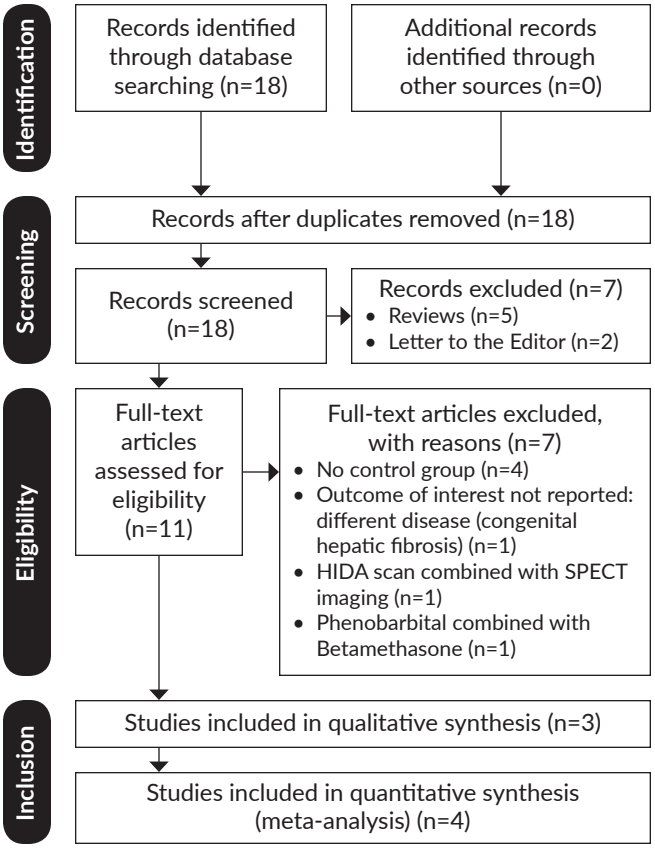
APPENDICES



Appendix 1. PRISMA diagram of included studies in the efficacy, effectiveness, and safety of phenobarbital in cholestasis.



Appendix 2. PRISMA diagram of included studies of HIDA Scan with phenobarbital premedication to diagnose obstructive jaundice.

Appendix 3. Appraisal of Included Studies

Phenobarbital as Treatment of Cholestasis

Joanna Briggs Institute Critical Appraisal Tool for Case Reports

	Thompson and Williams[5]
1. Were patient's demographic characteristics clearly described?	Y
2. Was the patient's history clearly described and presented as a timeline?	Y
3. Was the current clinical condition of the patient on presentation clearly described?	Y
4. Were diagnostic tests or assessment methods and the results clearly described?	Y
5. Was the intervention(s) or treatment procedure(s) clearly described?	Y
6. Was the post-intervention clinical condition clearly described?	Y
7. Were adverse events (harms) or unanticipated events identified and described?	N
8. Does the case report provide takeaway lessons?	Y
Overall Assessment	FAIR

Y – Yes, N – No

Joanna Briggs Institute Critical Appraisal Tool for Case Series

	Thompson 1967[10]	Linarelli 1973[6]	Bloomer 1975[7]	Nemeth 1990[9]	Ghent 1978[8]
1. Were there clear criteria for inclusion in the case series?	Y	Y	Y	Y	Y
2. Was the condition measured in a standard reliable way for all participants included in the case series?	Y	Y	Y	Y	Y
3. Were valid methods used for identification of the condition for all participants included in the case series?	Y	Y	Y	Y	Y
4. Did the case series have consecutive inclusion of participants?	U	U	U	U	N
5. Did the case series have complete inclusion of participants?	U	U	U	U	U
6. Was there clear reporting of the demographics of the participants in the study?	Y	Y	Y	Y	Y
7. Was there clear reporting of clinical information of the participants?	Y	Y	Y	Y	Y
8. Were the outcomes or follow up results of cases clearly reported?	Y	Y	Y	Y	Y
9. Was there clear reporting of the presenting site/clinic demographic information?	N	N	N	N	N
10. Was statistical analysis appropriate?	NA	NA	NA	NA	NA
Overall Assessment	FAIR	FAIR	FAIR	FAIR	FAIR

U – Unclear, Y – Yes, N – No, NA – Not applicable

Newcastle Ottawa Quality Assessment Scale for Cohort Studies

	Lewis 2018[18]
Selection (4 stars)	
1. Representativeness of exposed cohort (one star)	*
2. Selection of non exposed cohort (one star)	*
3. Ascertainment of exposure (one star)	*
4. Demonstration that outcome of interest was not present at the start (one star)	*
Comparability (2 stars)	
1. Comparability of cohorts on the basis of design or analysis controlled for confounders	
a. Study controls for age, sex, marital status; study controls for other factors (one star)	
b. Study controls for other factors (one star)	*
c. Cohorts is not comparable on the basis of the design or analysis controlled for confounders	
Outcome (3 stars)	
1. Assessment of outcome (independent blind assessment, record linkage, self report, no description) (one star)	
2. Was follow up long enough for outcomes to occur? (Yes or No). Yes (one star)	Not stated
3. Adequacy of follow up of cohorts	
a. Complete follow up of all subjects accounted for (one star)	*
b. Subjects lost to follow up unlikely to introduce bias - numbers lost <20% of those lost and those followed up (one star)	*
c. Follow up rate <80% and no description of lost to follow up	

Summary of Domains	
Selection	****
Comparability	*
Outcome	**
Overall Assessment	GOOD

Cochrane Risk of Bias for Randomized Trials

	Maldonado 2010[19]	Vajro 1986[20]
Risk of bias arising from randomization process	Some concerns	High
Risk of bias from intended interventions	Some concerns	High
Missing outcome data	Low risk	Low risk
Risk of bias in measurement of outcome	Low risk	High risk
Risk of bias in selection of reported result	Low risk	High risk
Overall Risk of Bias	Some concerns	High risk

Phenobarbital as a Premedication for Hepatobiliary Scintigraphy

Joanna Briggs Institute Critical Appraisal Tool for Diagnostic Accuracy

	Kwatra 2013[11]	Khorasani 2009[12]	Kirks 1984[13]	Ben-Haim 1995[14]
1. Was consecutive or random samples enrolled?	Y	Y	Y	Y
2. Was a case control design avoided?	Y	Y	Y	Y
3. Did the study avoid inappropriate exclusions?	Y	Y	Y	Y
4. Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y
5. If a threshold was used, was it pre-specified?	NA	NA	NA	NA
6. Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y
7. Were the reference standard results interpreted without knowledge of the results of the index test?	Y	N	Y	Y
8. Was there an appropriate interval between index test and reference standard?	Y	Y	Y	Y
9. Did all the patients receive the same reference standard?	Y	N	N	N
10. Were all the patients included in the analysis?	Y	Y	Y	N
Overall Assessment	INCLUDE	INCLUDE	INCLUDE	INCLUDE
Risk of Bias	Low	High	High	High

Y – Yes, N – No, NA – Not applicable

Newcastle Ottawa Quality Assessment Scale for Cohort Studies

	Charearnrad 2003[15]	Majd 1981[16]
Selection (4 stars)		
1. Representativeness of exposed cohort (one star)	*	*
2. Selection of non exposed cohort (one star)	*	*
3. Ascertainment of exposure (one star)	*	*
4. Demonstration that outcome of interest was not present at the start (one star)	*	*
Comparability (2 stars)		
1. Comparability of cohorts on the basis of design or analysis controlled for confounders a. Study controls for age, sex, marital status; study controls for other factors (one star) b. Study controls for other factors (one star) c. Cohorts is not comparable on the basis of the design or analysis controlled for confounders	*	*

Outcome (3 stars)		
1. Assessment of outcome (independent blind assessment, record linkage, self report, no description) (one star)	Not stated	*
2. Was follow up long enough for outcomes to occur? (Yes or No). Yes (one star)		
3. Adequacy of follow up of cohorts		
a. Complete follow up of all subjects accounted for (one star)	*	*
b. Subjects lost to follow up unlikely to introduce bias - numbers lost <20% of those lost and those followed up (one star)	*	*
c. Follow up rate <80% and no description of lost to follow up		
Summary of Domains		
Selection	****	****
Comparability	*	*
Outcome	**	***
Overall Assessment	GOOD	GOOD

Cochrane Risk of Bias for Randomized Trials

	Malik 2015[17]
Risk of bias arising from randomization process	Some concerns
Risk of bias from intended interventions	Some concerns
Missing outcome data	Some concerns
Risk of bias in measurement of outcome	High risk
Risk of bias in selection of reported result	High risk
Overall Risk of Bias	High risk

Appendix 4. Characteristics of Included Studies

Case reports/Case series

Author	Number of patients	Age of patients	Phenobarbital dose and duration	Diagnosis	Outcome reported
Thompson (1967)	4	45, 67, 56, 48 years	180 mg per day from 22 to 50 days	Post necrotic cirrhosis – 1 Primary biliary cirrhosis – 3 (one with sarcoidosis also)	Fall in plasma bilirubin level by about 60% of initial level by 10 to 14 days after treatment Other effects: decrease in itching and improvement in well being. **Side effect: All four patients had drowsiness and lethargy.**
Thompson and Williams (1970)	1	1 month	20 to 30 mg per day for 60 days	Intrahepatic biliary atresia	Plasma bilirubin decreased from 8.6 to 3.5 mg/dL when Phenobarbital was started and then increased again up to 12 mg/dL when it was stopped.
Linarelli (1973)	5	11, 7, 3, 4 and 2 months old	6 to 12 mg/kg/day from 3 to 7 months	Intrahepatic biliary atresia – 4 Extrahepatic biliary atresia – 1	No significant decrease in serum bilirubin. Clinical improvement in terms of relief of pruritus, decrease in size of xanthomas and 50% reduction in total cholesterol and lipid levels.
Bloomer (1975)	15 (3 Pediatrics at 2, 4 and 12 years old)	2 to 58 years	Adults: 120-250 mg/day Pedia: 3 to 5 mg/kg/day given from 2 to 5 months	Cholestatic hepatitis – 3 Primary biliary cirrhosis – 7 Sclerosing cholangitis – 2 Intrahepatic biliary hypoplasia – 3	Total serum bilirubin (mg/dL) Before: 7.0 ± 2.6 After: 3.6 ± 1.0 (p<0.01) Baseline serum total bilirubin decreased from 4 to 70% in 9 of 11 adults and from 40 to 60% in all three children. One patient with primary biliary cirrhosis had no jaundice. **Other effects**: Improvement in severity of pruritus in 11 of 13 patients with pruritus at onset (two had no pruritus at onset). Two of the three pediatric patients had some improvement of the pruritus
Ghent (1978)	2	24, 49 months	Dose to maintain Phenobarbital level: 5 mg/dl	Progressive intrahepatic cholestasis (brothers) – 2	Effect after 21 months: Patient 1: TB from 13.3 to 4.5 mg/dL Patient 2: TB from 22 to 14 mg/dL Both patients have dramatic improvement of pruritus
Nemeth (1990)	4	4, 7, 13 and 43 months	10 mg/kg/day from 1 to 4 months	Chronic intrahepatic cholestasis, unknown etiology – 3 Arteriohepatic dysplasia – 1	Slight improvement in total bilirubin but not normal levels. **Other effects:** Liver function such as the ALT, AST, GGT and AP deteriorated. Pruritus improved in 2 of 4 patients

Appendix 4. Characteristics of Included Studies *(continued)*

Author	Site	Study Design	N	Population	Dose		Results (with cholestasis)	
Maldonado	Mexico, Mexico	Randomized cross over clinical trial	18 patients (36 treatment)	Premature patients with TPN for two weeks DB >34 umol/L Weight 1-2 kg during the first 15 days of life Enteral intake >100 ml/kg/day	UDCA: 10 mg/kg/day Phenobarbital: 3 mg/kg/day	UDCA decreases DB in Neonatal cholestasis while Phenobarbital has no effect	Phenobarbital (n=18) 5.43 ± 2.63 6.07 ± 3.70 0.50 Mean difference: 0.67 (-1.5 to 2.8) Cross over study: 6.05 ± 2.50 5.7 ± 0.91 0.30 0.35 (-0.92, 1.62)	UDCA (n=18) 6.65 ± 3.28 4.36 ± 1.13 0.01 0.63 to 3.95 4.4 ± 2.1 2.7 ± 0.91 0.05 1.7 (0.604, 2.8)
Lewis	Missouri, Kansas City	Retrospective cohort	68	Infants with DB> 3.0 mg/dL (51.34) umol/L secondary to various medical diagnosis Treated with Ursodiol or Phenobarbital for at least 1 week	Not stated	Ursodeoxycholic acid was significantly more effective in reducing direct bilirubin than Phenobarbital (-33.35 vs 13.85 µmol/L) even after controlling for DB at the start of treatment and after all other variables were considered (-36.94 vs +4.62 µmol/L)	Phenobarbital (n=37) Change in DB (µmol/l) after adjusting DB at the start +13.85 Change in DB (µmol/l) after adjusting for all other factors +4.62	UDCA (n=31) -33.35 -36.94
Vajro	Bicetre, France	Randomly assigned	80 Group 1 (n=38) (operative success): 38 patients (16 Pb; 12 Cholestryramine; 10 controls Group 2 (n=42): (operative failure): 11 Pb; 15 Cholestyramine and 16 controls	Infants with extrahepatic biliary atresia who underwent operation: 56 with hepatoportoenterostomy 20 with hepato-portocholecystostomy 4 with cystojejunostomy	Phenobarbital: 7.5 to 10 mg/kg/day Cholestyramine: 4 grams per day	No significant difference in the 3 subgroups with regards decrease in total bilirubin and cholesterol levels Side effect: appearance of rickets in two children (group not specified) despite parenteral Vit. D supplement		

Phenobarbital as a premedication in HIDA scan

Author	Site	Study Design	Radiotracer	N	Population	Dose	Results	Adverse effects
Malik (2015)	Kashmir, India	Prospective cohort wherein treatment was randomly assigned	Technetium 99m trimethyl-bromo-iminodiacetic acid (Mebrofenin)	50 non excretor in HIDA scan 20 Pb; 20 UDCA; 10 controls	Diagnosed with Neonatal cholestasis Syndrome (not specified whether NH or BA) who were Non excretors in HIDA scan	Phenobarbital 5 mg/kg/day for 5 days UDCA: 20 mg/kg/day for 5 days Normal saline drops for 5 days (n=10)	Phenobarbital: 2/20 became excreters UDCA: 1/20 became excreters Normal saline: 1/10 became excreter	
Khorasani (2009)	Kermanshah, Iran	Randomized cross over trial (diagnostic study)	Technetium 99m trimethyl-bromo-iminodiacetic acid (Mebrofenin)	30 consecutive children with final diagnosis of BA: 13; NH: 17	Infants with neonatal cholestasis	Phenobarbital: 5 mg/kg BID x 5 days UDCA: 20 mg/kg/day BID x 5 days	Validity of HIDA scan for BA: Phenobarbital: 100% sensitivity: 13/13; specificity: 11/17 (65%) UDCA: 100% sensitivity: 13/13; specificity: 16/17 (94%)	Adverse effect: All patients – lethargy, poor feeding, irritability, hypotonia, which resolved with discontinuation of the drug.

Appendix 4. Characteristics of Included Studies *(continued)*

Phenobarbital as a premedication in HIDA scan

Author	Site	Study Design	Radiotracer	N	Population	Dose	Results	Adverse effects
Charearnrad (2003)	Bangkok, Thailand	Retrospective cohort	Technetium 99m diisoprophyl iminodiacetic acid	95 cholestatic infants treated as follows: Group 1 (n=48): Phenobarbital 5 mg/kg/day x 5 days Group 2 (n=29): Phenobarbital less than 5 mg/kg/day for less than 5 days Group 3: No treatment	Cholestatic infants with or without Phenobarbital	Phenobarbital 5 mg/kg/day or less for 5 days or less or no treatment	For BA for both treated and untreated with Phenobarbital 100% sensitivity and specificity with or without Phenobarbital For NH (treated): 66% sensitivity; 100% specificity For NH (untreated): 100% sensitivity; 100% specificity	
Ben Haim (1995)	Iowa, USA	Prospective cohort (diagnostic study)	Technetium 99m trimethyl-bromo-iminodiacetic acid (Mebrofenin)	37 patients with conjugated hyperbilirubinemia	37 patients with conjugated hyperbilirubinemia 8 with BA 29 with non BA	Phenobarbital at 5 mg/kg/day for 2 to 28 days given to 17 patients with non BA No group with no treatment	In 29 with non BA, no difference in the time to visualize the bowels in those who were treated with Phenobarbital and those who were not. (Mean ± SEM: 6 ± 1.9 hrs vs 5.5 ± 2)	
Majd (1981)	Washington DC, USA	Prospective cohort	Technetium 99m diisoprophyl iminodiacetic acid	Group 1 (n=16): No treatment Group 2 (n=24): Phenobarbital treatment	40 jaundiced infants with conjugated hyperbilirubinemia	Phenobarbital 5 mg/kg/day for 3 to 7 days No treatment	With treatment: Sensitivity for BA: 100%; (10/10) Specificity: 93% (13/14) No treatment: Sensitivity for BA: 100% (4/4) Specificity: 85% (6/7)	
Kirks (1984)	Durham, North Carolina	Prospective cohort (diagnostic study)	Technetium 99m diisoprophyl iminodiacetic acid	15 infants <3 months	Fifteen patients with conjugated hyperbilirubinemia	Phenobarbital 5 mg/kg/day	Neonatal hepatitis: (n=7) presence of excretion in 5 and absence in 2 with severe neonatal hepatitis Biliary atresia (n=7): no excretion Choledochal cyst (n=1): accumulation of tracer in porta hepatis	
Kwatra (2013)	Washington, USA	Retrospective cohort (diagnostic study)	Technetium 99m trimethyl-bromo-iminodiacetic acid (Mebrofenin)	186 children (BA=43; non BA= 143) with 210 hepatobiliary scans	Cholestatic Infants <130 days of life with HIDA scan	Phenobarbital 5 mg/kg/day x 5 days to achieve serum level of >15 µcg/ml No group with no treatment	Validity of HIDA scan for BA: 100% sensitivity (43/43); 93% specificity (133/143) If neonatal hepatitis group only: 100% sensitivity (43/43); 93% specificity (78/82): 95%	