



Effect of Pre-exchange Transfusion Albumin Infusion on Neonatal Hyperbilirubinemia: A Meta-analysis of Randomized Clinical Trials

Fang Pan^{#1}, Ying Xue Wang^{#2}, Juan Xie³, Yan Xiao Liu^{3,*} and Xin He^{3,**}

¹Department of Pediatric Surgery, Children's Hospital of Nanjing Medical University, Nanjing, China

²Department of Pharmacy, Yantai Yantaishan Hospital, Shandong, China

³Department of Pharmacy, Women's Hospital of Nanjing Medical University, Nanjing Maternity and Child Health Care Hospital, Nanjing, China

*Corresponding author: Department of Pharmacy, Women's Hospital of Nanjing Medical University, Nanjing Maternity and Child Health Care Hospital, Nanjing, China. Email: xiaoyliu@163.com

**Corresponding author: Department of Pharmacy, Women's Hospital of Nanjing Medical University, Nanjing Maternity and Child Health Care Hospital, Nanjing, China. Email: hexin19870422@163.com

These authors are contributed equally as the first author.

Received 2022 June 27; Revised 2022 August 04; Accepted 2022 August 07.

Abstract

Background: This study was carried out to systematically evaluate the efficacy and safety of pre-exchange transfusion (pre-ET) albumin infusion on neonatal hyperbilirubinemia.

Methods: A comprehensive search of relevant studies from EMBASE, Medline, Cochrane Register of Controlled Trials, ClinicalTrials.gov, China National Knowledge Infrastructure, Wei Pu Information, Wan Fang Data, and Chinese Biomedical Literature Database was conducted from inception to December 2021. Two different authors screened the titles, abstracts, and full texts of the articles. The quality of the included trials was assessed independently by two different authors according to the Cochrane Collaboration's Risk of Bias. The data were analyzed and compiled using Review Manager software (RevMan version 5.3).

Results: In total, four studies enrolling 195 neonates were included in this review. The quality of the included studies was deemed fair to good. The meta-analysis showed that pre-ET albumin infusion was superior to exchange transfusion (ET) alone for reducing the need for repeating ET (risk ratio (RR) = 0.25, 95% confidence interval (CI): 0.09 - 0.72, I-squared (I^2) = 8%; fixed effects model) and shortening the duration of phototherapy (PT) (mean difference (MD) = -11.46 hours, 95% CI: -16.56 to -6.36, I^2 = 93%; random effects model (REM)). No significant differences were detected between the two groups for post-ET total serum bilirubin (TSB) at 6 hours (MD = -3.51 mg/dL, 95% CI: -7.93 - 0.93, I^2 = 97%; REM) and 12 hours (MD = -4.21 mg/dL, 95% CI: -9.08 - 0.65, I^2 = 99%; REM). None of the patients developed acute bilirubin encephalopathy in any of the trials. No death prior to hospital discharge was reported in any trials, and no adverse effects were observed in intervention groups.

Conclusions: Based on four studied trials, pre-ET albumin infusion appears to be safe and effective in reducing the need for repeating ET and shortening PT duration. These potential benefits, including the reduction of post-ET TSB, need to be revalidated in future trials using rigorous methodology.

Keywords: Human Albumin, Neonatal Hyperbilirubinemia, Neonatal Jaundice, Meta-analysis

1. Context

Jaundice is one of the most common disorders affecting newborns and one of the major reasons for re-admission during the neonatal period (1). Neonatal jaundice is characterized by the yellowish hyperpigmentation of the skin, mucous membranes, or organs (2). The pathogeny of neonatal jaundice is hyperbilirubinemia (identified as total serum bilirubin (TSB) at least 171 $\mu\text{mol/L}$ for premature neonates or at least 256 $\mu\text{mol/L}$ for term neonates) (2). Neonatal jaundice occurs in up to 60 - 80% of preterm and term neonates and in 10% of breast-feeding neonates (3). Severe hyperbilirubinemia increases the risk

of complications or brain disorders in neonates (4). These complications include a wide range of mild-to-severe clinical conditions, such as bilirubin-induced neurologic dysfunction, bilirubin encephalopathy or acute bilirubin encephalopathy, and kernicterus (4). Globally, it is predicted that severe hyperbilirubinemia influences at least 481,000 near-term or term neonates annually, more than 63,000 cases of whom survive with moderate or severe disability (5, 6). Thus, appropriate evaluations and therapeutic interventions to prevent and/or reduce bilirubin-induced neurotoxicity are urgently needed (7).

Several guidelines were provided by the American

Academy of Pediatrics for the management of neonatal jaundice (8). Conventional therapies for this disease include standard phototherapy (PT), intensive PT, albumin infusion, and/or exchange transfusion (ET). Currently, PT is a noninvasive, acceptable, safe, and effective treatment (9). However, light exposure to PT might result in water loss, hypocalcemia, circadian rhythms disorder, allergic diseases, or the occurrence of new melanocytic nevi (10). In addition, intensive PT might lead to the photo-oxidation of albumin, resulting in a decrease or complete inhibition of binding affinity for bilirubin (11). The ET is indicated in severe neonatal hyperbilirubinemia when other standard therapeutic strategies, such as PT, have failed and the risk of acute bilirubin encephalopathy is high (12).

Albumin infusion has been used as an adjuvant therapy to PT or prior to ET, improving the outcomes of neonatal hyperbilirubinemia (13). Studies have evaluated the effect of albumin infusion prior to ET with respect to bilirubin removal, the clinical outcomes of which showed variable results. Shahian and Moslehi reported that an infusion of 1 g/kg albumin one hour prior to ET could significantly reduce the post-ET TSB and the duration of PT (14). Nevertheless, Chan and Schiff observed no significant difference in bilirubin removal following albumin infusion prior to ET (15). Given that albumin is a blood product and a scarce and expensive resource, its administration could increase the potential risk of infection and adverse reactions. Albumin infusion might also induce several potential side effects, including fluid overload. However, a systematic review of albumin infusion in preterm neonates revealed no sufficient evidence to consider albumin infusion being associated with significant adverse reactions.

2. Objectives

The present study aimed to assess the efficacy and safety of pre-exchange transfusion (pre-ET) albumin infusion for neonatal hyperbilirubinemia.

3. Methods

3.1. Eligibility Criteria

The study protocol (CRD42018117279) was registered on PROSPERO (<https://www.crd.york.ac.uk/prospero/>). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct the meta-analysis. Eligibility criteria were based on the PICOS format. The population included neonates within 28 days of birth with hyperbilirubinemia. The intervention involved PT with human albumin infusion prior to ET. The comparator was PT without human albumin infusion

prior to ET. The outcomes included post-ET TSB at 6 and 12 hours, the incidence of acute bilirubin encephalopathy, the need for repeating ET, the duration of PT (hour), death prior to hospital discharge, and the incidence of adverse reactions during albumin infusion. Moreover, the study design included randomized controlled trials (RCTs). The diagnostic criteria for neonatal jaundice followed international guidelines (8, 16).

3.2. Search Strategy

Relevant studies from China National Knowledge Infrastructure, Wei Pu Information, Wan Fang Data, Chinese Biomedical Literature Database, EMBASE, Medline, Cochrane Register of Controlled Trials, and ClinicalTrials.gov were explored. The following Medical Subjects and Headings (MeSH) terms and keywords were used:

(1) "Albumins"

(2) "Hyperbilirubinemia" or "Bilirubinemia" or "Jaundice" or "Bilirubin" or "Hematoidin" or "Bilirubinate" or "Icterus"

(3) "Infant" or "Newborn" or "Neonate"

The above-mentioned terms were used separately or combined using the string terms "OR" and "AND". All published articles from inception to 31st December 2021 were retrieved.

3.3. Screening and Selection of Studies

Two different authors independently screened the articles according to the eligibility criteria listed above. A third author resolved any controversy in the process.

3.4. Data Extraction

The first author's information and publication year, sample size, study design, inclusion/exclusion criteria, criteria for conducting ET, control groups, intervention groups, intervention dosage, gestational age, birth weight, and outcomes were extracted by two different authors independently.

The primary outcomes were post-ET TSB at 6 and 12 hours and the incidence of acute bilirubin encephalopathy. The secondary outcomes included the need for repeating ET, the duration of PT (hour), death prior to hospital discharge, and the incidence of adverse reactions during albumin infusion.

3.5. Quality Assessment Methods

The Cochrane Collaboration's Risk of Bias (17), including seven items, was applied by two authors to evaluate the quality of the included studies. The quality of the studies was assessed as low risk, high risk, or unclear risk (17). A third author resolved any disagreements by discussion.

3.6. Statistical Analysis

The data were analyzed and compiled using Review Manager software (RevMan version 5.3, The Cochrane Collaboration, 2011). Risk ratio (RR) and 95% confidence interval (CI) were calculated for dichotomous data; nevertheless, mean difference (MD) was used for continuous data. I-squared (I^2) statistics were used to perform the heterogeneity tests, and a P-value less than 0.05 was considered statistically significant. For $I^2 \geq 75\%$, significant heterogeneity was considered, and a random effects model (REM) was selected; otherwise, a fixed effects model (FEM) (18) was adopted.

3.7. Publication Bias

When there were more than 10 included studies in a meta-analysis, publication bias was detected using Funnel plots (19).

4. Results

4.1. General Description of Overall Studies

A total of 7441 citations were retrieved using the search strategy described above. After the removal of duplications, 6473 articles remained. After screening the titles and abstracts, 82 full-text articles were retrieved and reassessed for eligibility. Finally, four studies met the inclusion criteria and were included in the systematic review (Figure 1).

The four included trials (13, 14, 20, 21) involved 195 neonatal jaundice participants. All participants in the intervention groups were given intravenous albumin infusion combined with ET; nonetheless, the participants in the control groups were given a placebo combined with ET. During the period of albumin infusion, all the participants in both groups were given PT. In three of the trials (14, 20, 21), the participants were administered 20% human albumin; nevertheless, 5% human albumin was used in only one of the trials (13). In all studies, albumin was used prior to ET at a dosage of 1 g per kilogram body weight. Table 1 shows a summary of the characteristics of the included studies.

4.2. Assessment of Risk of Bias

Overall, the quality of the included studies was deemed fair to good (Figure 2). Most included studies specified the sequence generation process and reported allocation concealment. All blinding of participants and personnel was assessed as low risk, except for one trial in which odd numbers were used for the control group and even numbers for the albumin group. The blinding of outcome assessment was also assessed as low risk in all trials, as blinding did not affect the measurement of TSB. All studies were reported

with low attrition bias, as none of the participants was lost to follow-up. Reporting bias was assessed as low risk in all studies. None of the studies was observed to be at high risk of for-profit bias. The detailed information is summarized in Table 2.

4.3. Effects of Intervention

4.3.1. Post-exchange Transfusion Total Serum Bilirubin Levels at 6 and 12 Hours

Three trials, in which 153 neonates were enrolled, provided information on post-ET TSB levels at 6 and 12 hours. The REM was used for the primary analysis. The meta-analysis showed no statistically significant difference for post-ET TSB at 6 hours (MD = -3.51 mg/dL, 95% CI: -7.93 - 0.93, $I^2 = 97\%$; REM) (Figure 3A). For post-exchange TSB at 12 hours, there was also no statistically significant difference (MD = -4.21 mg/dL, 95% CI: -9.08 - 0.65, $I^2 = 99\%$; REM) (Figure 3B).

4.3.2. Acute Bilirubin Encephalopathy

No patients developed acute bilirubin encephalopathy in any of the trials.

4.3.3. Need for Repeating Exchange Transfusion

Four trials, in which 195 neonates were enrolled, provided information on the neonates who required repeating ET. In the meta-analysis, a statistically significant difference was observed between the two groups for this outcome. Pre-exchange transfusion albumin infusion was observed to be superior to no albumin infusion for reducing the need for repeating ET (RR = 0.25, 95% CI: 0.09 - 0.72, $I^2 = 8\%$; FEM) (Figure 4).

4.3.4. Duration of Phototherapy (Hour)

All trials reported the duration of PT. The meta-analysis revealed that pre-ET albumin infusion was associated with a shorter duration of PT (MD = -11.46 hours, 95% CI: -16.56 to -6.36, $I^2 = 93\%$; REM) (Figure 5).

4.3.5. Incidence of Death Prior to Hospital Discharge

No death prior to hospital discharge was reported in any of the trials.

4.3.6. Adverse Reactions During Albumin Infusion

Four studies addressed adverse events, and no adverse effects were observed in the intervention groups.

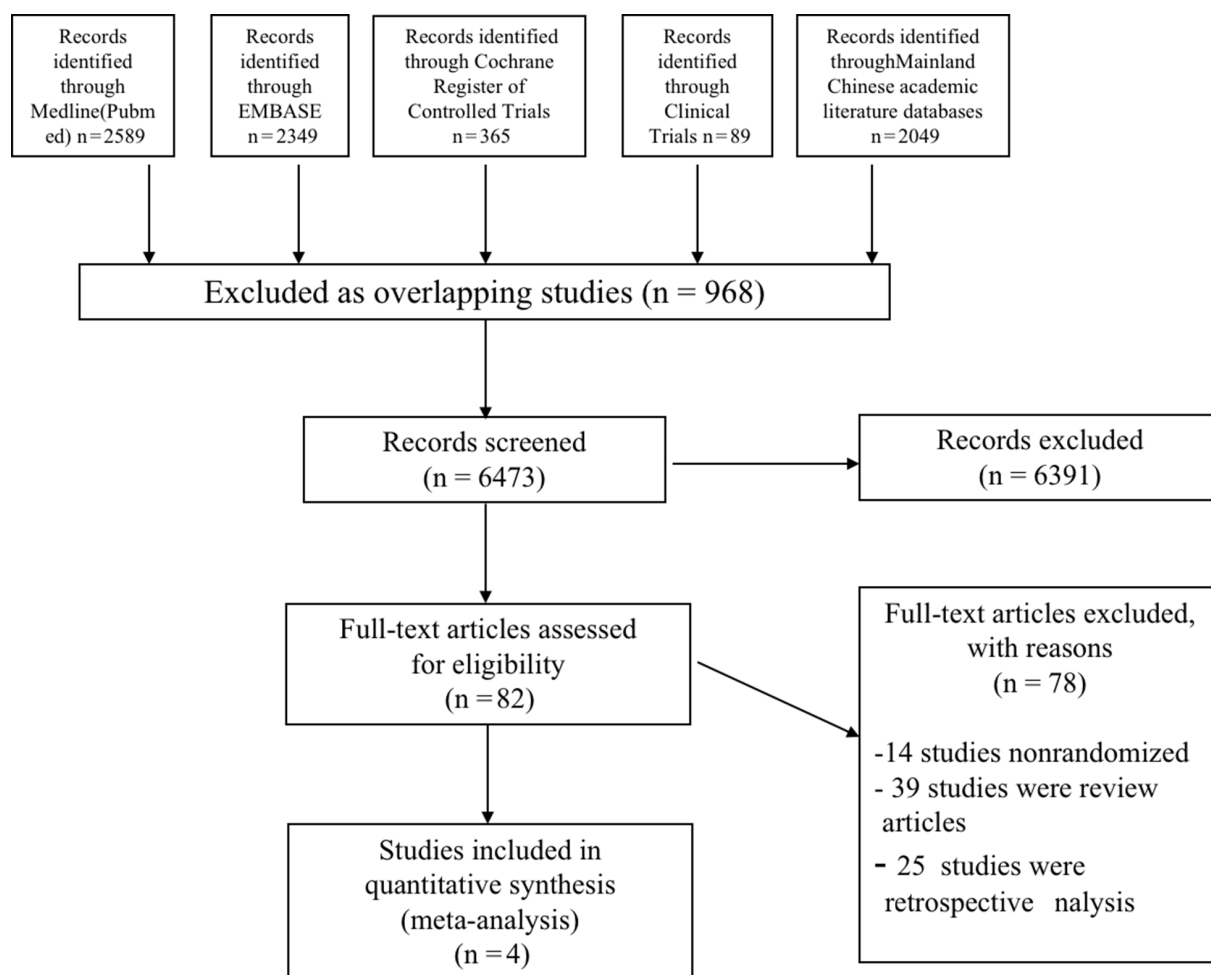


Figure 1. Study flowchart

5. Discussion

5.1. Summary of Main Findings

The study focused on assessing the safety and efficacy of pre-ET albumin infusion for the treatment of neonatal hyperbilirubinemia. Four RCTs were included, most of which were evaluated with a low risk of bias. Only three studies reported the primary outcome of post-ET TSB at 6 and 12 hours. All the included trials focused on the effects of pre-ET albumin infusion on the need for repeating ET and PT duration. The present meta-analysis demonstrated that pre-ET albumin infusion could reduce the need for repeating ET and shorten the duration of PT; however, there was no statistically significant difference in post-ET TSB at 6 and 12 hours between the two groups.

Severe hyperbilirubinemia can lead to brain damage, which is caused by unconjugated bilirubin (UCB) (8). The

small amount of UCB, which is not bound to albumin, can pass the blood-brain barrier and disrupt several essential cellular functions, inducing apoptosis, necrosis, kernicterus, or death (22, 23). Therefore, early detection and treatment are important in the prevention of bilirubin-induced encephalopathy. At physiological pH, UCB is poorly water-soluble and needs to be metabolized, which includes being bound to albumin as a dianion at a primary binding site in the liver and then excreted from the body. Furthermore, Wood et al. showed that intensive PT for severe hyperbilirubinemia could cause the photo-oxidation of albumin, thereby leading to the decrease or complete inhibition of its binding affinity for UCB (11). More binding sites need to be provided for UCB to reduce UCB levels, which ultimately decreases the risk of central nervous system toxicity. Therefore, in theory, it is possible to avoid UCB accumulation in the brain by increasing

Table 1. Description of Characteristics, Baseline, and Outcomes of Four Randomized Controlled Trials Included in This Meta-analysis

N	Study (First Author, Year)	Sample	GA (Week) ^a	Birth Weight (g) ^a	Age on Admission (day) ^a	Criteria to ET	Intervention Group	Dosage of Albumin	Control Group	Endpoints	
1	Alharis et al., 2020 (21)					Follows AAP guidelines for exchange transfusion	20% human albumin combined with ET	A dose of 1 g/kg	ET	Post-ET TSB levels at 6 and 12 hours; acute bilirubin encephalopathy; need for repeating ET; duration of PT; incidence of death prior to hospital discharge; adverse reactions during albumin infusion	
		Treatment	24	38.62 ± 0.78	3122 ± 296						5.6 ± 0.99
		Control	29	38.25 ± 0.8	3091 ± 262						5.2 ± 0.98
2	Dash et al., 2015 (20)					When two TSB values at least 4 hours apart were 2 mg/dL or more below the PT threshold for that postnatal age	20% human albumin combined with ET	A dose of 1 g/kg	0.9% saline at 5 mL/kg combined with ET	Post-ET TSB levels at 6 and 12 hours; acute bilirubin encephalopathy; need for repeating ET; duration of PT; incidence of death prior to hospital discharge; adverse reactions during albumin infusion	
		Treatment	23	38.2 ± 1.5	2952 ± 382						4.98 ± 2.47
		Control	27	37.7 ± 1.7	2926 ± 626						4.46 ± 1.75
3	Mitra et al., 2011 (13)					Defined as the inability to produce a decline of 1 to 2 mg/dL within 4 hours after the initiation of PT	5% human albumin combined with ET	A dose of 1 g/kg	Intravenous fluid at 20 mL/kg combined with ET	Post-ET UCB levels at 6 and 12 hours; acute bilirubin encephalopathy; need for repeating ET; duration of PT; incidence of death prior to hospital discharge; adverse reactions during albumin infusion	
		Treatment	21	34.5 ± 1.65	1619 ± 324						6.23 ± 1.6
		Control	21	34 ± 1.6	1660 ± 320						6.67 ± 1.43
4	Shahian and Moselehi, 2010 (14)					The inability to produce a decline of 1 to 2 mg/dL within 4 hours after the initiation of PT	20% human albumin combined with ET	A dose of 1 g/kg	ET	Post-ET TSB levels at 6 and 12 hours; acute bilirubin encephalopathy; need for repeating ET; duration of PT; incidence of death prior to hospital discharge; adverse reactions during albumin infusion	
		Treatment	25	39.3 ± 1.2	3239 ± 585						7 ± 1.1
		Control	25	39.5 ± 1.5	3264 ± 428						8 ± 1.0

Abbreviations: N, number; GA, gestational age; ET, exchange transfusion; AAP, American Academy of Pediatrics; TSB, total serum bilirubin; PT, phototherapy; UCB, unconjugated bilirubin.

^a Values are expressed as mean ± standard deviation.

bilirubin-binding capacity within the intravascular compartment by albumin infusion. The current meta-analysis also demonstrated that pre-ET albumin infusion can reduce the need for repeating ET and shorten the duration of PT, thereby validating the efficacy of pre-ET albumin infusion for neonatal hyperbilirubinemia.

Furthermore, the level of UCB in plasma can be decreased by albumin within the intravascular space, allowing unbound tissue bilirubin to move into the plasma to establish equilibration between plasma bilirubin and the extravascular space (24, 25). Albumin infusion prior to ET resulted in more efficient removal of intravascular UCB, a consequent reduction in TSB, and a lower rebound increase in post-ET UCB (26). Nevertheless, the post-ET TSB levels at 6 and 12 hours of the intervention group were not significantly different from those of the control group. Why did the post-ET TSB at 6 and 12 hours not decrease after pre-ET albumin infusion? It is likely that the level of post-ET TSB depends on both pre-ET extravascular and vascular bilirubin levels and that the relationship between TSB and extravascular bilirubin levels was obscured due to significant variations in vascular bilirubin-albumin interactions (27). As a result, despite similar pre-ET UCB in two groups, there

could be variations in extravascular bilirubin levels, eventually affecting the final outcome (28). In addition, albumin infusion for neonatal hyperbilirubinemia might have increased the non-binding fraction of serum albumin; nevertheless, the ratio of bilirubin to albumin might have remained the same (29). Therefore, it follows that an estimation of UCB is important, and the assessment of the level of UCB might be more appropriate for evaluating the efficacy of pre-ET albumin infusion in neonatal hyperbilirubinemia.

On the other hand, three of all the included trials provided information on post-ET TSB levels at 6 and 12 hours. Only one trial showed that the administration of 1 g/kg of 20% albumin prior to ET is not superior to 0.9% saline in reducing post-ET TSB levels at 6 and 12 hours (20). Notably, the aforementioned study (20) had a lower baseline serum albumin level than two other studies (14, 21) (2.8 vs. 3.2 - 3.4 g/dL). It was possible that 1 g/kg of 20% albumin was not enough to provide sufficient binding sites for bilirubin due to a lower baseline serum albumin level, leading to not observing an increase in bilirubin removal following ET. Earlier studies with a positive effect of albumin infusion had higher baseline serum albumin levels (3 - 3.5 g/dL),

Table 2. Risk of Bias for Included Studies

Bias	Authors' Judgment	Support for Judgment
Shahian and Moslehi, 2010 (14)		
Random sequence generation (selection bias)	Low risk	The random numbers were computer generated.
Allocation concealment (selection bias)	Low risk	Slips bearing the allocated group were placed in serially numbered, opaque, sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Twenty-five neonates in the intervention group received intravenous 20% human albumin one hour before exchange; nevertheless, the control group only underwent a blood exchange.
Blinding of outcome assessment (detection bias)	Low risk	TSB was measured every 6 hours for both groups during the first 24 hours following the exchange using a Unistat® bilirubinometer.
Incomplete outcome data (attrition bias)	Low risk	None
Selective reporting (reporting bias)	Low risk	Undiscovered
Other types of bias	Low risk	Undiscovered
Mitra et al., 2011 (13)		
Random sequence generation (selection bias)	Low risk	Randomization was performed using statistical software.
Allocation concealment (selection bias)	Low risk	Slips containing the allocated group were placed in serially numbered sealed envelopes.
Blinding of participants and personnel (performance bias)	Unclear risk	The infusion of 5% albumin solution was performed for newborns in the intervention group 2 hours before the exchange transfusion. The intravenous maintenance fluid at 20 mL/kg was administered to newborns in the control group for 2 hours.
Blinding of outcome assessment (detection bias)	Unclear risk	Two senior pediatricians clinically examined the newborns for evidence of patent ductus arteriosus, necrotizing enterocolitis, and pulmonary edema independently. K-statistics was utilized to evaluate inter-observer variations in evaluating the severity of birth asphyxia and albumin infusion-associated complications.
Incomplete outcome data (attrition bias)	Low risk	None
Selective reporting (reporting bias)	Low risk	Undiscovered
Other types of bias	Low risk	Undiscovered
Dash et al., 2015 (20)		
Random sequence generation (selection bias)	Low risk	Randomization into two groups was based on a web-generated random number sequence.
Allocation concealment (selection bias)	Low risk	Allocation was concealed in opaque, sealed envelopes which were kept by a person not involved in any other aspect of the study.
Blinding of participants and personnel (performance bias)	Low risk	Separate personnel, in a separate room away from the patient care area, prepared the study drug. Blinding was ensured using special black-colored, completely opaque syringes and brown-colored opaque extension intravenous tubing for loading and administration of study drugs.
Blinding of outcome assessment (detection bias)	Low risk	Investigators, members of the treatment team, and laboratory technicians remained masked during the intervention.
Incomplete outcome data (attrition bias)	Low risk	None
Selective reporting (reporting bias)	Low risk	Undiscovered
Other types of bias	Low risk	Undiscovered
Alharis et al., 2020 (21)		
Random sequence generation (selection bias)	Unclear risk	Randomization was performed by taking the odd numbers as the control group and even numbers as the albumin group.
Allocation concealment (selection bias)	High risk	Taking the odd numbers as the control group and even numbers as the albumin group
Blinding of participants and personnel (performance bias)	High risk	Taking the odd numbers as the control group and even numbers as the albumin group
Blinding of outcome assessment (detection bias)	Low risk	TSB was measured by drawing blood using heparinized capillary tubes by pricking the heel and then centrifuged with serial number 0000526-01.00 with 1000 rounds per minute and then placed in a bilirubinometer.
Incomplete outcome data (attrition bias)	Low risk	None
Selective reporting (reporting bias)	Low risk	Undiscovered
Other types of bias	Low risk	Undiscovered

Abbreviation: TSB, total serum bilirubin.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alharis FM 2020	?	-	-	+	+	+	+
Dash N 2015	+	+	+	+	+	+	+
Mitra S 2011	+	+	?	?	+	+	+
Shahian M 2010	+	+	-	+	+	+	+

Figure 2. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study

and albumin levels were usually at least 5 g/dL after infusion (14, 15, 26, 30). A higher baseline serum albumin level could provide more binding sites for bilirubin and might facilitate the diffusion of bilirubin into intravascular space better. Whether the dose of albumin priming needs to be determined according to baseline serum albumin levels or whether larger doses of albumin for those neonates with low baseline serum albumin levels need to be used should be evaluated. Therefore, the results about not observing an increase in bilirubin removal following ET need more well-designed large RCTs to be revalidated.

5.2. Strengths and Limitations

The current study has been the first meta-analysis to show that pre-ET albumin infusion can reduce the need for repeating ET and shorten the duration of PT; however, there was no statistically significant difference between the two groups with respect to post-ET TSB at 6 and 12 hours. The present study included a very limited number of only four relevant RCTs. Therefore, more RCTs with larger population sizes are urgently needed to validate the efficacy of

pre-ET albumin infusion for neonatal hyperbilirubinemia. In addition, this meta-analysis demonstrated that pre-ET albumin infusion could shorten the duration of PT; nevertheless, very high heterogeneity was observed among studies ($I^2 = 93\%$). This might be due to the differences in the production of albumin, types of PT, or the manufacture of used bilirubinometer.

Furthermore, an important limitation might be a history of intravenous fluid supplementation in most study subjects before the intervention. Intravenous fluid supplementation could result in a faster drop in TSB levels due to its effects on volume expansion and glomerular filtration rate (31, 32). The effect of intravenous fluid supplementation on bilirubin-albumin binding and the movement of bilirubin across capillaries remains unclear. Some studies report an increase in the removal of bilirubin after infusion with 1 g/kg of albumin 1 - 4 hours prior to ET (13, 14, 33); however, other studies were unable to demonstrate similar effects (15, 30, 34). In addition, albumin infusion leads to volume expansion, which could also independently cause a reduction of bilirubin level after administration (25). To confirm the hypothesis that albumin infusion might enhance the removal of bilirubin through bilirubin binding, the confounding effect of the volume expansion of albumin infusion has to be counterbalanced by using a mother fluid. Most of the included studies did not use any mother fluid. Therefore, further well-designed large RCTs are needed to assess the efficacy of albumin infusion.

5.3. Implications for Further Studies

Based on the present meta-analysis, pre-ET albumin infusion might result in short-term benefits, including reducing the need for repeating ET and shortening the duration of PT. However, all of the included studies were not large-scale, multi-centered trials. It is suggested to conduct future studies to assess the aforementioned outcomes, especially post-ET TSB levels. Moreover, whether to use larger doses of albumin for those neonates with low baseline serum albumin levels needs to be evaluated. The efficacy and safety of pre-ET albumin infusion need to be further elucidated.

5.4. Conclusions

Based on four studied trials, pre-ET albumin infusion appears to be safe and effective in reducing the need for repeating ET and shortening the duration of PT. However, due to limitations of the number and types of studies, there is a need for further well-designed, large RCTs to explore the efficacy and safety of pre-ET albumin infusion for neonates with hyperbilirubinemia before being able

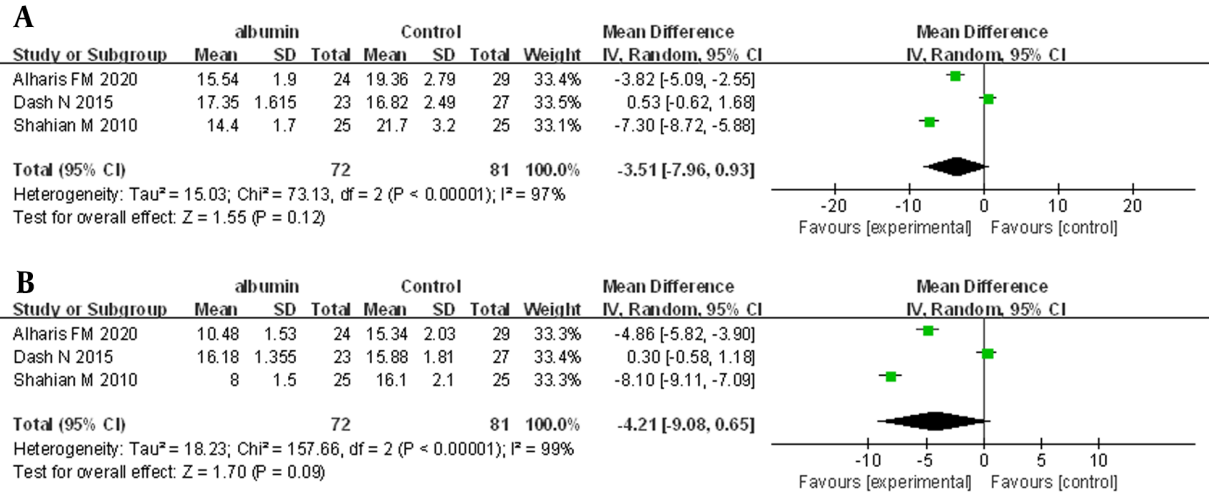


Figure 3. Effect of pre-exchange transfusion (pre-ET) albumin infusion on reduction of post-ET total serum bilirubin (TSB) (mg/dL); A, effect of pre-ET on reduction of post-ET TSB (mg/dL) at 6 hours; B, effect of pre-ET on reduction of post-ET TSB (mg/dL) at 12 hours

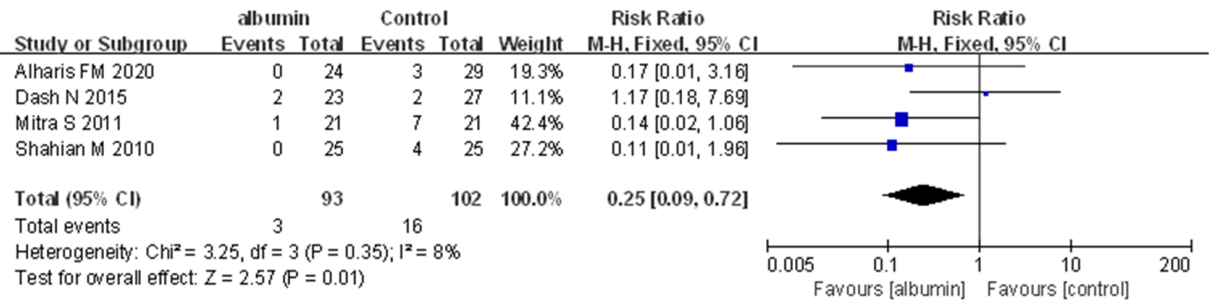


Figure 4. Effect of pre-exchange transfusion (pre-ET) albumin infusion on reduction of need for repeating ET

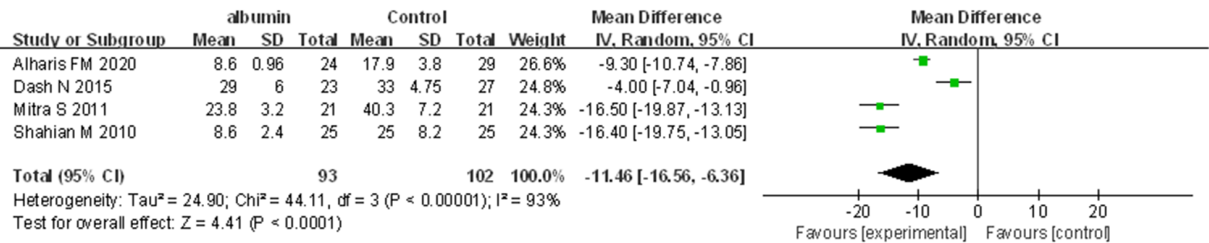


Figure 5. Effect of pre-exchange transfusion (pre-ET) albumin infusion on shortening phototherapy duration

to make a conclusive recommendation about pre-ET albumin infusion for the treatment of neonatal hyperbilirubinemia.

Acknowledgments

The authors would like to express their gratitude to Professor Cheng for his excellent work in this study.

Footnotes

Authors' Contribution: Xin He and Xueying Wang conceived and designed the evaluation and drafted the manuscript. Fang Pan participated in designing the evaluation, performed parts of the statistical analysis, and helped draft the manuscript. Xiaoyan Liu re-evaluated the clinical data, performed the statistical analysis, and revised the manuscript. Juan Xie collected the clinical data, interpreted them, and revised the manuscript. Xin He re-analyzed the clinical and statistical data and revised the manuscript. All the authors read and approved the final manuscript.

Conflict of Interests: The authors declare no conflicts of interest.

Data Reproducibility: No new data were created or analyzed in this study. Data sharing does not apply to this article.

Funding/Support: This study was not supported by any funding.

References

- Fakhri M, Farhadi R, Mousavinasab N, Hosseinimehr SJ, Yousefi SS, Davoodi A, et al. Preventive effect of purgative manna on neonatal jaundice: A double blind randomized controlled clinical trial. *J Ethnopharmacol.* 2019;**236**:240–9. [PubMed ID: 30853647]. <https://doi.org/10.1016/j.jep.2019.03.009>.
- Wu RH, Feng S, Han M, Caldwell P, Liu SG, Zhang J, et al. Yinzhihuang oral liquid combined with phototherapy for neonatal jaundice: a systematic review and meta-analysis of randomized clinical trials. *BMC Complement Altern Med.* 2018;**18**(1):228. [PubMed ID: 30055615]. [PubMed Central ID: PMC6064068]. <https://doi.org/10.1186/s12906-018-2290-x>.
- Asefa GG, Gebrewahid TG, Nuguse H, Gebremichael MW, Birhane M, Zereabruk K, et al. Determinants of Neonatal Jaundice among Neonates Admitted to Neonatal Intensive Care Unit in Public General Hospitals of Central Zone, Tigray, Northern Ethiopia, 2019: a Case-Control Study. *Biomed Res Int.* 2020;**2020**:4743974. [PubMed ID: 33145350]. [PubMed Central ID: PMC7596433]. <https://doi.org/10.1155/2020/4743974>.
- Bhutani VK; Committee on Fetus and Newborn; American Academy of Pediatrics. Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2011;**128**(4):e1046–52. [PubMed ID: 21949150]. <https://doi.org/10.1542/peds.2011-1494>.
- Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F, et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. *Pediatr Res.* 2013;**74 Suppl 1**:86–100. [PubMed ID: 24366465]. [PubMed Central ID: PMC3873706]. <https://doi.org/10.1038/pr.2013.208>.
- Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, et al. Every Newborn: progress, priorities, and potential beyond survival. *Lancet.* 2014;**384**(9938):189–205. [PubMed ID: 24853593]. [https://doi.org/10.1016/S0140-6736\(14\)60496-7](https://doi.org/10.1016/S0140-6736(14)60496-7).
- Amin SB, Saluja S, Saili A, Laroia N, Orlando M, Wang H, et al. Auditory toxicity in late preterm and term neonates with severe jaundice. *Dev Med Child Neurol.* 2017;**59**(3):297–303. [PubMed ID: 27718221]. [PubMed Central ID: PMC5288130]. <https://doi.org/10.1111/dmnc.13284>.
- American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;**114**(1):297–316. [PubMed ID: 15231951]. <https://doi.org/10.1542/peds.114.1.297>.
- Hansen TW. Twists and turns in phototherapy for neonatal jaundice. *Acta Paediatr.* 2010;**99**(8):1117–8. [PubMed ID: 20528792]. <https://doi.org/10.1111/j.1651-2227.2010.01898.x>.
- Xiong T, Qu Y, Cambier S, Mu D. The side effects of phototherapy for neonatal jaundice: what do we know? What should we do? *Eur J Pediatr.* 2011;**170**(10):1247–55. [PubMed ID: 21455834]. <https://doi.org/10.1007/s00431-011-1454-1>.
- Wood B, Comley A, Sherwell J. Effect of additional albumin administration during exchange transfusion on plasma albumin-binding capacity. *Arch Dis Child.* 1970;**45**(239):59–62. [PubMed ID: 5440206]. [PubMed Central ID: PMC2020389]. <https://doi.org/10.1136/adc.45.239.59>.
- Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. *J Pediatr.* 2002;**140**(4):396–403. [PubMed ID: 12006952]. <https://doi.org/10.1067/mpd.2002.123098>.
- Mitra S, Samanta M, Sarkar M, De AK, Chatterjee S. Pre-exchange 5% albumin infusion in low birth weight neonates with intensive phototherapy failure—a randomized controlled trial. *J Trop Pediatr.* 2011;**57**(3):217–21. [PubMed ID: 20823089]. <https://doi.org/10.1093/tropej/fmq083>.
- Shahian M, Moslehi MA. Effect of albumin administration prior to exchange transfusion in term neonates with hyperbilirubinemia—a randomized controlled trial. *Indian Pediatr.* 2010;**47**(3):241–4. [PubMed ID: 19578230]. <https://doi.org/10.1007/s13312-010-0046-x>.
- Chan G, Schiff D. Variance in albumin loading in exchange transfusions. *J Pediatr.* 1976;**88**(4 Pt 1):609–13. [PubMed ID: 1255322]. [https://doi.org/10.1016/s0022-3476\(76\)80020-0](https://doi.org/10.1016/s0022-3476(76)80020-0).
- Amos RC, Jacob H, Leith W. Jaundice in newborn babies under 28 days: NICE guideline 2016 (CG98). *Arch Dis Child Educ Pract Ed.* 2017;**102**(4):207–9. [PubMed ID: 28179382]. <https://doi.org/10.1136/archdischild-2016-311556>.
- Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;**343**:d5928. [PubMed ID: 22008217]. [PubMed Central ID: PMC3196245]. <https://doi.org/10.1136/bmj.d5928>.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;**21**(11):1539–58. [PubMed ID: 12119191]. <https://doi.org/10.1002/sim.1186>.
- Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med.* 2001;**20**(4):641–54. [PubMed ID: 11223905]. <https://doi.org/10.1002/sim.698>.
- Dash N, Kumar P, Sundaram V, Attri SV. Pre exchange Albumin Administration in Neonates with Hyperbilirubinemia: A Randomized Controlled Trial. *Indian Pediatr.* 2015;**52**(9):763–7. [PubMed ID: 26519710]. <https://doi.org/10.1007/s13312-015-0713-z>.

21. Alharis FM, Albakaa AA, Jumaah Nasrawi A, Shuaib AM. The role of Albumin infusion before exchange transfusion in term neonates with hyperbilirubinemia. *J Int Pharm Res.* 2020;**12**(3). <https://doi.org/10.31838/ijpr/2020.12.03.182>.
22. Ahlfors CE, Amin SB, Parker AE. Unbound bilirubin predicts abnormal automated auditory brainstem response in a diverse newborn population. *J Perinatol.* 2009;**29**(4):305–9. [PubMed ID: 19242487]. [PubMed Central ID: PMC4285409]. <https://doi.org/10.1038/jp.2008.199>.
23. Ostrow JD, Pascolo L, Brites D, Tiribelli C. Molecular basis of bilirubin-induced neurotoxicity. *Trends Mol Med.* 2004;**10**(2):65–70. [PubMed ID: 15102359]. <https://doi.org/10.1016/j.molmed.2003.12.003>.
24. Hosono S, Ohno T, Kimoto H, Nagoshi R, Shimizu M, Nozawa M, et al. Follow-up study of auditory brainstem responses in infants with high unbound bilirubin levels treated with albumin infusion therapy. *Pediatr Int.* 2002;**44**(5):488–92. [PubMed ID: 12225546]. <https://doi.org/10.1046/j.1442-200x.2002.01612.x>.
25. Tsao YC, Yu VY. Albumin in management of neonatal hyperbilirubinaemia. *Arch Dis Child.* 1972;**47**(252):250–6. [PubMed ID: 5023474]. [PubMed Central ID: PMC1648058]. <https://doi.org/10.1136/adc.47.252.250>.
26. Odell GB, Cohen SN, Gordes EH. Administration of albumin in the management of hyperbilirubinemia by exchange transfusions. *Pediatrics.* 1962;**30**:613–21. [PubMed ID: 13939465].
27. Ahlfors CE, Wennberg RP, Ostrow JD, Tiribelli C. Unbound (free) bilirubin: improving the paradigm for evaluating neonatal jaundice. *Clin Chem.* 2009;**55**(7):1288–99. [PubMed ID: 19423734]. <https://doi.org/10.1373/clinchem.2008.121269>.
28. Ahlfors CE. Pre exchange transfusion administration of albumin: an overlooked adjunct in the treatment of severe neonatal jaundice? *Indian Pediatr.* 2010;**47**(3):231–2. [PubMed ID: 20371891]. <https://doi.org/10.1007/s13312-010-0041-2>.
29. Ebbesen F, Brodersen R. Albumin administration combined with phototherapy in treatment of hyperbilirubinaemia in low-birth-weight infants. *Acta Paediatr Scand.* 1981;**70**(5):649–53. [PubMed ID: 7324912]. <https://doi.org/10.1111/j.1651-2227.1981.tb05762.x>.
30. Comley A, Wood B. Albumin administration in exchange transfusion for hyperbilirubinaemia. *Arch Dis Child.* 1968;**43**(228):151–4. [PubMed ID: 5645688]. [PubMed Central ID: PMC2019852]. <https://doi.org/10.1136/adc.43.228.151>.
31. Saini SS, Kumar P, Balasubramaniam K, Mehta S. Fluid supplementation in hyperbilirubinemia. *Indian J Pediatr.* 2011;**78**(9):1096–9. [PubMed ID: 21373828]. <https://doi.org/10.1007/s12098-011-0394-0>.
32. Mehta S, Kumar P, Narang A. A randomized controlled trial of fluid supplementation in term neonates with severe hyperbilirubinemia. *J Pediatr.* 2005;**147**(6):781–5. [PubMed ID: 16356431]. <https://doi.org/10.1016/j.jpeds.2005.07.026>.
33. Kitchen WH, Krieger VI, Smith MA. Human albumin in exchange transfusion. A quantitative study of the influence of added human albumin on bilirubin removal. *J Pediatr.* 1960;**57**:876–83. [PubMed ID: 13756466]. [https://doi.org/10.1016/s0022-3476\(60\)80137-0](https://doi.org/10.1016/s0022-3476(60)80137-0).
34. Ruys JH, Van Gelderen HH. Administration of albumin in exchange transfusion. *J Pediatr.* 1962;**61**:413–7. [PubMed ID: 14495533]. [https://doi.org/10.1016/s0022-3476\(62\)80372-2](https://doi.org/10.1016/s0022-3476(62)80372-2).