Research Paper

Efficacy and Safety of Yinzhihuang Granule Combined with Phototherapy in Neonatal Pathological Jaundice Treatment: A Meta-Analysis

NA ZHENG SHEN, D. WANG[1] AND L. FAN*

Department of Pediatrics, Institute of Chinese Medical Literature and Culture, [1]College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong 250355, China

To assess the efficacy and safety of Yinzhihuang granule combined with phototherapy in neonatal pathological jaundice treatment. By searching China network knowledge infrastructure, Wan Fang database, Virtual IP address database, Virtual IP, PubMed, EmBase together with the Cochrane library until March 31st, 2022. Literatures on Yinzhihuang combined with phototherapy in neonatal pathological jaundice treatment were collected. Literatures were screened by the inclusion and exclusion criteria and data were extracted. A total of 19 literatures were included in this study, a total of 2221 neonates with pathological jaundice. The outcomes of meta-analysis demonstrated the total clinical effective rate of Yinzhihuang combined with phototherapy in neonatal pathological jaundice treatment was significantly higher than that of phototherapy. At the end of one course of treatment, the total bilirubin level was significantly lower than that of the phototherapy group. The recovery time and hospital stay were shorter than those in the phototherapy group. The occurrence rate of adverse reactions was reduced compared to that of phototherapy group and the difference was significant. Yinzhihuang granule combined with phototherapy in neonatal pathological jaundice treatment has better clinical effect and safety.

Key words: Yinzhhuang, pathological jaundice, phototherapy, curative effect, bilirubin

Neonatal jaundice refers to the aberrant metabolism of bilirubin and the clinical manifestations are yellow staining of skin, mucosa and even sclera caused by the elevated level of bilirubin in blood. It can be divided into pathological jaundice and physiological jaundice. It is one of the common pediatric diseases. In recent years, its incidence is increasing year by year[1]. Excessive bilirubin in the neonatal period can cause brain neuropathy (namely bilirubin encephalopathy), which is manifested as not eating, not drinking and not making any disturbance. It is the most serious complication of pathological jaundice in the newborn, with serious condition and high mortality and permanent nerve damage can be caused to the nerves[2]. The incidence of pathological jaundice in neonates is high in China. It is important to detect and effectively judge the nature of jaundice in time, diagnose and treat early, and prevent the occurrence of bilirubin encephalopathy. At present, the treatment of pathologic jaundice includes phototherapy, drug therapy and supportive therapy. Phototherapy is a common clinical treatment, including intermittent and continuous blue light irradiation. The treatment of drugs usually include probiotics (Mamaiai, Peifeikang, etc.), glucose powder, Yinzhihuang granule, which is the first choice for neonatal pathological jaundice treatment. Yinzhihuang granule is a preparation made of extracts of 4 kinds of traditional Chinese medicine, namely *Artemisia*, *Gardenia*, honeysuckle and *Scutellaria*. It has the effects of detoxification, dampness, heat clearing and allopathy. It is often used in the treatment of liver diseases in clinic and has been frequently used in neonatal pathological jaundice treatment in the last few years[3-5]. Yinzhihuang granule by regulating bilirubin metabolism reduces the absorption of bilirubin, reduce the occurrence rate of adverse drug reactions and shorten the treatment time. In recent years, a number of literatures have compared the efficacy and safety of Yinzhihuang combined with phototherapy and phototherapy in neonatal pathological jaundice therapy[6-24]. This study intended to collect domestic and foreign published studies on the efficacy and/or safety of Yinzhihuang combined with phototherapy and phototherapy in neonatal jaundice therapy and conducted a meta-analysis to assess the clinical efficacy and safety of Yinzhihuang combined phototherapy.

***Address for correspondence**
E-mail: a13188908541@163.com

MATERIALS AND METHODS

Inclusion criteria:

The clinical Randomized Controlled Trials (RCTs) of Yinzhihuang granule combined with phototherapy in neonatal pathological jaundice treatment were published at home and abroad. The study subjects met the diagnostic criteria of pathological jaundice in practical pediatrics at the age of 4 w after birth.

Intervention measures: The experimental group was treated with oral Yinzhihuang granules+phototherapy (blue light irradiation therapy), the control group was only treated with phototherapy, allowing patients to take symptomatic treatment when necessary (prevention of infection, relief of diarrhea, nutritional supplementation, etc.,).

Outcome index: The primary outcome index was clinical efficacy, which was determined according to the level of serum total bilirubin. Including four grades cure, special effect, effective and ineffective. Secondary outcome measures included direct bilirubin, indirect bilirubin, recovery time (defined as the time from onset to resolution of jaundice) and adverse drug reactions. Among them, the clinical effect was determined according to the clinical efficacy judgment standard of neonatal pathological jaundice in pediatrics.

The total effective rate=Significant efficiency+effective rate

Exclusion criteria:

The subjects had physiologic jaundice, hepatobiliary diseases or other hereditary diseases; non-randomized, non-clinical studies, retrospective studies, repeated literature, conference abstracts, reviews, individual cases, review literature; poorly designed studies with no outcome measures, incomplete and/or extractable outcome data, no control group, non-Chinese and English literature.

Search strategy:

China Network Knowledge Infrastructure (CNKI), Wan fang Data, Virtual IP Address, PubMed, Embase and Cochrane Library databases were searched to collect RCTs of Yinzhihuang granule combined with phototherapy in neonatal pathological jaundice therapy. The search time limit was from March 31st, 2022. The search method of combining subject words and free words was used. The search words were Yinzhihuang granule, jaundice and the English search words were Yinzhihuang, jaundice and so on.

Literature selection and data extraction:

Two researchers screened the literature based on the inclusion and exclusion criteria, extracted data, discussed and decided by a third party in case of disagreement. End note X7 was used for literature screening to eliminate duplicate documents and irrelevant literature was excluded by reading the title and abstract. Finally, the full text was read to determine the included literature based on the inclusion criteria and exclusion criteria. The included literature was read through and extracted; title, author name, published literature, sample size and baseline data (age, gender, etc.,) of the experimental group and the control group, study type and intervention measures and outcome indicators.

Literature quality evaluation:

By Cochrane RevMan5.3 software risk bias tool for quality evaluation into the literature including seven items. The generation of random sequence and allocation concealment (perpetrators and participants), double blind and ending index evaluation personnel blinded, incomplete data, publication bias, other bias, each project bias risk include: low risk, uncertain and high risk.

Statistical analysis:

RevMan5.3 software was used for meta-analysis. Relative Risk (RR) was used for enumeration data and Standard Mean Difference (SMD) was used for measurement data. When $I2 \leq 50$ %, $p > 0.05$, the possibility of heterogeneity was small and the fixed effect model was used. When $I2 > 50$ % and $p \leq 0.05$, heterogeneity was indicated and subgroup analysis or random effect model analysis was used. The pooled statistic was $p < 0.05$ to indicate statistical significance.

RESULTS AND DISSCUSION

As displayed in fig. 1, a total of 886 articles were included in the primary selection, containing 189 articles from CNKI, 404 articles from Wan fang, 216 articles from VIP, 7 articles from PubMed, 2 articles from Embase and 68 articles from Cochrane Library. Based on the inclusion criteria, the most popular 19 articles were included in the meta-analysis *via* reading the title, abstract and full text. The basic information of the included literature was indicated in Table 1.

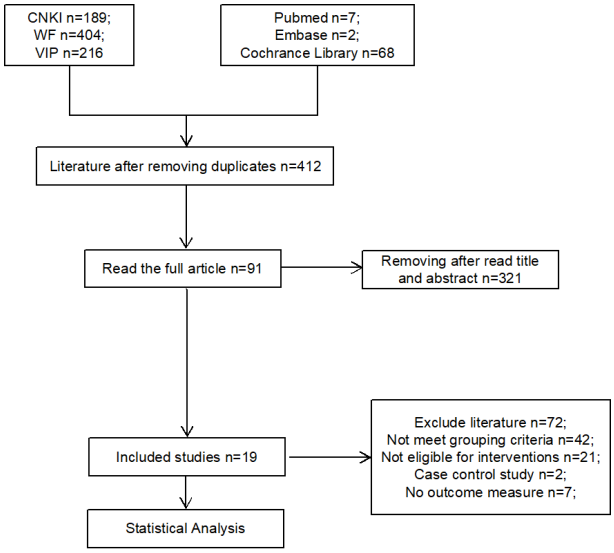

Fig. 1: Literature screening process

TABLE 1: BASIC INFORMATION OF THE INCLUDED LITERATURE

Included studies	Sample size (male/female)		Average age (day)		Intervening measure		Yin Zhihuang dose	Course of treatment (Day)	Outcome indicator
	T	C	T	C	T	C			
Fengmin *et al.*[6]	23/16	21/18	10.43±3.86	10.15±3.69	Yinzhihuang granules+intermittent blue light irradiation+live binary *Bacillus subtilis*	Intermittent blue light irradiation+live binary *Bacillus subtilis*	3 g/d	5	(1) (2) (4)
Li *et al.*[7]	46/29	48/27	5.32±1.35	5.28±1.34	Yinzhihuang granule+intermittent blue light irradiation	Intermittent blue light irradiation	3 g/d	7	(1) (2) (5) (7)
Hongguang *et al.*[8]	24/18	23/19	10.69±1.63	10.74±1.85	Yinzhihuang granule+blue light irradiation+ *Saccharomyces boulardii* sachets	Blue light irradiation+ Saccharomyces *boulardii sachets*	3 g/d	5	(1) (4) (5)
Li *et al.*[9]	29/16	28/17	15.21±2.11	15.28±2.12	Yinzhihuang granule+ single blue light irradiation	Single blue light irradiation	7.5 ml/d	7	(1) (2) (4) (5) (7)
Chen *et al.* [10]	16/14	17/13	8.1±1.6	7.5±13	Yinzhihuang granule+ blue light irradiation	Blue light irradiation	NA	7	(1) (5)
Zhou *et al.*[11]	NA	NA	NA	NA	Yinzhihuang granule+ blue light irradiation	Blue light irradiation	3 g/d	6	(1) (2)
Bai *et al.*[12]	23/19	25/17	8.1±3.2	8.5±3.4	Yinzhihuang granule+ blue light irradiation	Blue light irradiation	3 g/d	5	(1) (4) (7)
Xiufang *et al.*[13]	48/25	47/27	5.31±1.02	5.11±1.03	Yinzhihuang granule+ intermittent blue light irradiation	Intermittent blue light irradiation	3 g/d	7	(1) (2) (6)(7)
Juan *et al.* [14]	40/35	39/36	NA	NA	Yinzhihuang granule+ blue light irradiation	Blue light irradiation	3 g/d	5	(1) (2) (4) (7)
Deyong *et al.*[15]	19/17	17/19	NA	NA	Yinzhihuang granule+ blue light irradiation	Blue light irradiation	4.5 g/d	7	(1) (6) (7)
Ying *et al.*[16]	31/24	32/23	7.11±1.16	7.01±1.12	Yinzhihuang granule+ blue light irradiation	Blue light irradiation	NA	6	(1) (2) (6)
Fang *et al.*[17]	32/28	32/28	5. 4±0. 9	6. 2±0. 7	Yinzhihuang granule+ blue light irradiation	Blue light irradiation	3 g/d	7	(1) (2) (4)

Yan *et al.*[18]	26/24	27/23	17.25±2.03	17.30±0.08	Yinzhihuang granule+blue light irradiation	Blue light irradiation	3 g/d	7	(1) (6) (7)
Huanan *et al.*[19]	28/13	23/18	15.13±6.87	15.41±6.91	Yinzhihuang granule+intermittent blue light irradiation	Intermittent blue light irradiation	3 g/d	7	(1) (2) (4) (5)
Xiaoli *et al.*[20]	31/15	29/17	7.0±2.3	7.2±2.5	Yinzhihuang granule+blue light irradiation	Blue light irradiation	3 g/d	7	(1) (3) (4) (6) (7)
Li *et al.*[21]	101/86	116/71	4.30±1.46	4.22±1.49	Yinzhihuang granule+pure blue light irradiation	Pure blue light irradiation	3 g/d	7	(1) (3) (4) (7)
Shan *et al.*[22]	37/28	38/27	14.2±2.0	14.2±1.9	Yinzhihuang granule+pure blue light irradiation	Pure blue light irradiation	3 g/d	7	(1) (2) (4)
Qibing *et al.*[23]	26/24	27/23	14.2±2.9	13.9±2.8	Yinzhihuang granule+pure blue light irradiation	Pure blue light irradiation	3 g/d	7	(1) (2) (7)
Jingli *et al.*[24]	29/20	31/18	10.63±5.17	10.85±5.31	Yinzhihuang granule+pure blue light irradiation	Pure blue light irradiation	3 g/d	7	(1) (2) (3) (7)

Note: (1): Clinical efficacy; (2): Bilirubin; (3): Total bile acids; (4): Recovery time; (5): Length of hospital stay; (6): Company with other and (7): Adverse reactions

The 19 included literatures all mentioned the specific method of randomization, complete outcome data and no selective reporting. No literatures mentioned the allocation hiding and whether it was double-blind (implementer and participant). The 3 literatures did not mention whether the outcome indicator evaluation was blinded, as shown in fig. 2.

A total of 16 studies were included, and the heterogeneity test showed that there was no significant heterogeneity among the studies (χ^2=17.39, p=0.30, I2=14 %). The fixed-effect model was utilized for analysis and the results were shown in fig. 3. The results unveiled a significant difference in the total effective rate between the two groups (RR=1.22, 95 % CI=(1.18,1.26), p<0.00001). The total effective rate of Yinzhihuang granule combined with phototherapy in neonatal pathological jaundice therapy was significantly higher than that of phototherapy.

A total of 16 studies were included and the heterogeneity test manifested a significant heterogeneity among the studies (χ^2=109.35, p<0.00001, I2=99 %). The random effect model was adopted to analyze the results, as indicated in fig. 4. The results demonstrated that the difference of serum total bilirubin level between the two groups was significant (SMD=-32.76, 95 % CI=(-38.30, -27.23), p<0.00001). The serum total bilirubin level of Yinzhihuang granule combined with phototherapy in neonatal pathological jaundice treatment was lower than that of phototherapy.

A total of 10 studies were included and the heterogeneity test showed a significant heterogeneity among the studies (χ^2=139.78, p<0.00001, I2=94 %). The random effects model was utilized to analyze the results, as shown in fig. 5. The results displayed that the difference of recovery time between the two groups was significant (SMD=-1.45, 95 % CI=(-2.01, -0.89), p<0.00001). Yinzhihuang granule combined with phototherapy in the treatment of neonatal pathological jaundice had a shorter recovery time than phototherapy. A total of 5 studies were included and the heterogeneity test showed that there was significant heterogeneity among the studies (χ^2=25.54, p<0.0001, I2=84 %). The random effect model was used for analysis and the results were shown in fig. 6. The analysis results showed that the difference of hospital stay between the two groups was statistically significant (SMD=-3.55, 95 % CI=(-4.65,-2.46), p<0.00001). Yinzhihuang granule combined with phototherapy in neonatal pathological jaundice treatment had a shorter hospital stay than phototherapy.

A total of 9 studies were included and the heterogeneity test exhibited a significant heterogeneity among the studies (χ^2=18.89, p=0.02, I2=58 %). The random effect model was adopted to analyze the results, as shown in fig. 7. The outcomes uncovered a significant difference in the occurrence rate of adverse reactions between the two groups (RR=0.53, 95 % CI=(0.30, 0.93), p=0.03). The occurrence rate of adverse reactions of Yinzhihuang granule combined with phototherapy in neonatal pathological jaundice treatment was lower

than that of phototherapy.

The funnel plot was drawn with the five outcome indicators of total clinical response rate, total serum bilirubin, recovery time, length of hospital stay, as well as adverse drug reactions, as shown in fig. 8. The results showed that the included literatures of total clinical response rate, recovery time and length of hospital stay were basically symmetrically distributed in the funnel plot, and the possibility of publication bias was small. The three items of serum total bilirubin and adverse drug reactions were not symmetrically distributed in the funnel plot, suggesting that there may be a large publication bias.

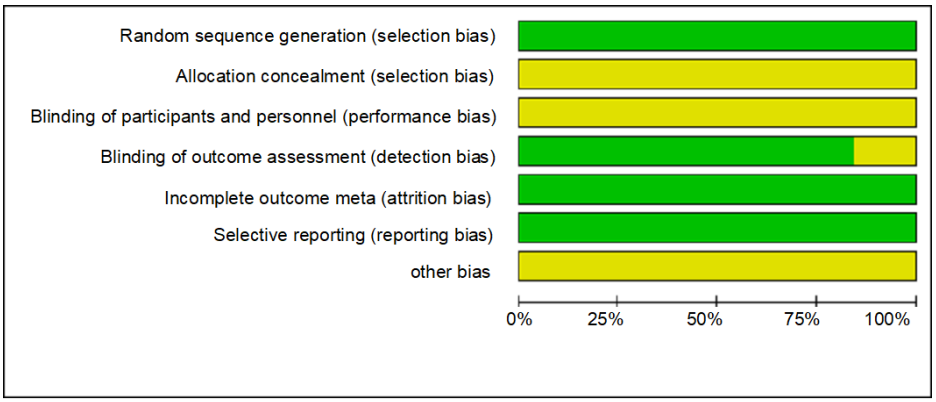

Fig. 2: Results of risk bias assessment
Note: (■): Low risk of bias; (■): Unclear risk of bias and (■): High risk of bias

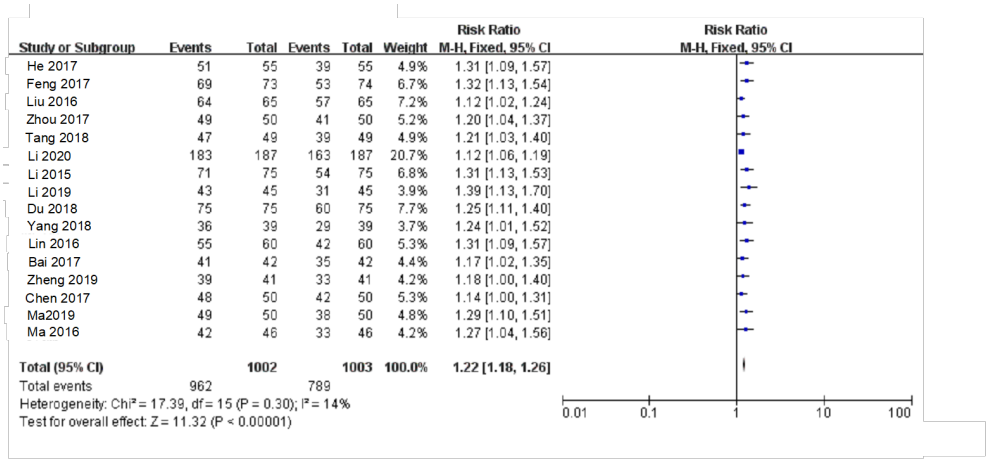

Fig. 3: Meta-analysis forest plot of clinical total effective rate analysis

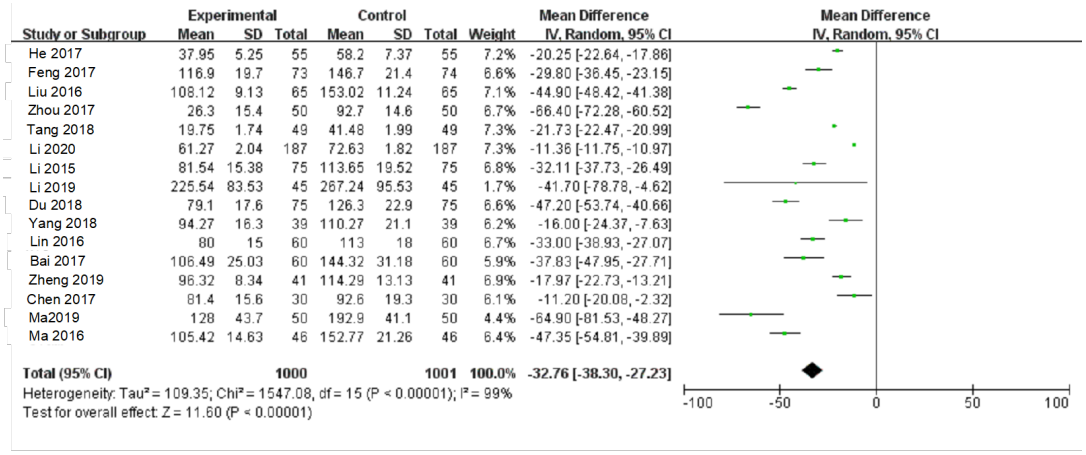

Fig. 4: Forest plot of meta-analysis of total bilirubin levels after 1 course of treatment

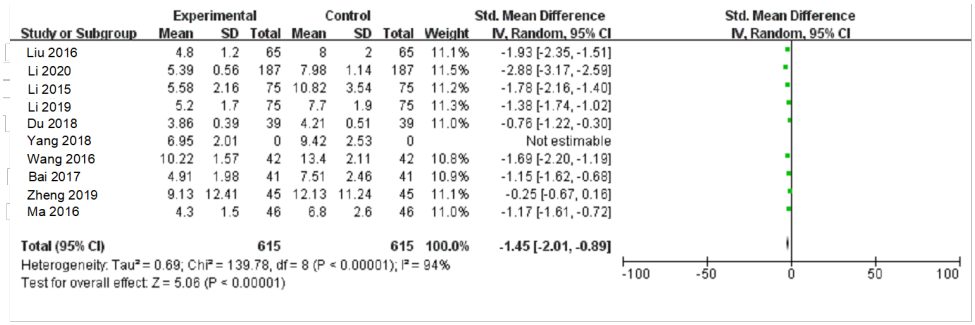

Fig. 5: Forest plot of recovery time meta-analysis

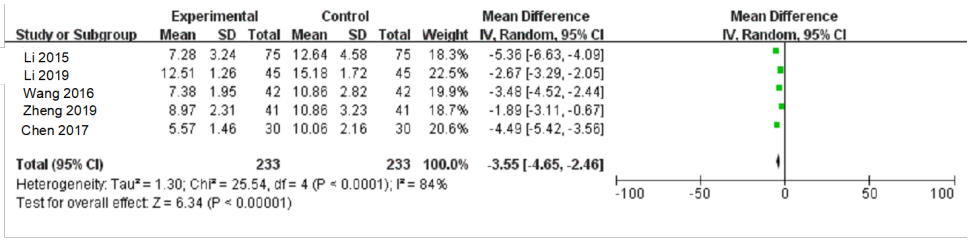

Fig. 6: Forest plot of hospital stay meta-analysis

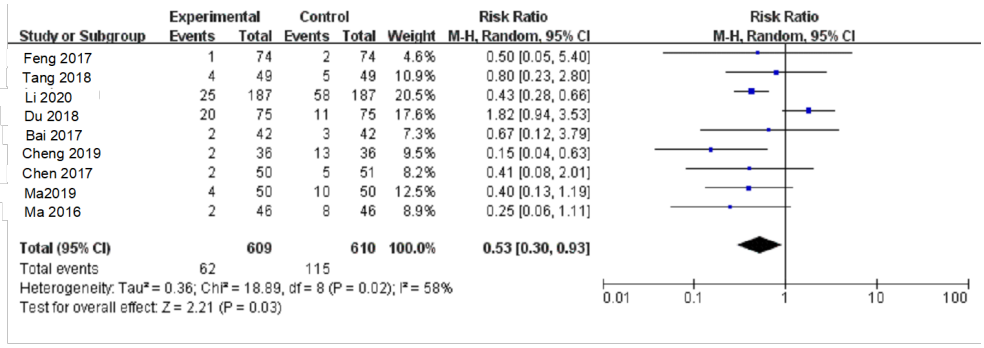

Fig. 7: Forest plot of meta-analysis of adverse drug reactions

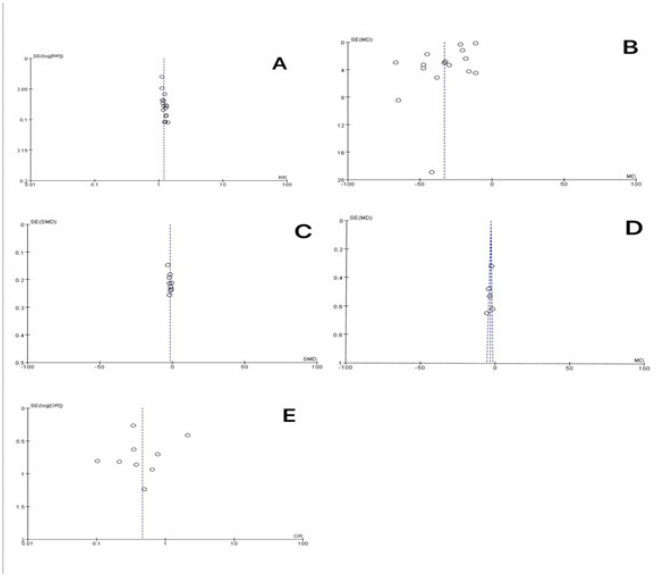

Fig. 8: Funnel chart of 5 indicators

According to traditional Chinese medicine, the pathogenesis of pathological jaundice is cold and dampness block, dampness and heat stasis, and bile overflow, which is related to cold and dampness, and dampness and heat[25]. Yinzhihuang granule comes from Yinchen Hao soup, 4 kinds of drugs synergistic effect, can get the effect of clearing heat and detoxifying, removing yellow and dampening, protecting liver and gallbladder. Yinzhihuang is used in the treatment of neonatal pathologic jaundice, but the sample size of the literature published in recent years is small. This study finally included 19 articles for research through screening, and the results showed that the treatment of Yinzhihuang combined with phototherapy in neonatal pathologic jaundice could effectively improve the clinical total effective rate, reduce serum total bilirubin level, shorten the recovery time and hospital stay. At the same time, the occurrence rate of adverse reactions was reduced and the safety was good.

Yinzhihuang granule has the function of protecting liver and gallbladder, by regulating Alanine Aminotransferase (ALT), total bile acid and other indicators, to achieve the role of regulating liver function. With the excretion of bilirubin in urine and feces, the jaundice is gradually subsided and the skin symptoms are improved. Some studies have shown that the main effects of Yinzhihuang granule can reduce bilirubin level[26]. Compared with injection, oral administration not only avoids allergy, but also avoids invasive operation. Besides, its antibacterial effect is improved and the destruction of red blood cells is reduced when combined with antibiotics. Moreover, it can inhibit body allergy, reduce red blood cell hemolysis. Experimental studies in rats with hyperbilirubinemia have showed that Yinzhihuang granules inhibit the increase of bilirubin by elevating the expression of organic anion transport polypeptide 1b2, multidrug resistance associated protein 2 and Uridine Diphosphate (UDP)-glucuronosyltransferase 1A1[27]. Some studies have shown that Yinzhihuang granule can promote the secretion and antagonism of bile, improve the levels of serum liver enzymes and accelerate the jaundice resolution time[28]. It can effectively reduce the level of bilirubin, improve the clinical efficiency, as well as shorten the recovery time and hospital stay. Yinzhihuang combined with phototherapy in neonatal pathological jaundice treatment has a significant clinical effect. In terms of safety, combination therapy has a lower occurrence rate of adverse reactions. The side effects of phototherapy include fever, diarrhea, skin rash erythema, testicular damage and dehydration, etc.,[29] while the side effects of Yinzhihuang are often manifested as diarrhea and vomiting, especially in patients with spleen deficiency and loose stool[30]. The above side effects are mild and can be relieved spontaneously after discontinuation of the drug. However, but the results of this study results indicated that Yinzhihuang combined with phototherapy treatment had lower occurrence rate of adverse reactions and better security[1-19]. In this study, all the included literatures adopted clear randomization method and reported complete data without high risk bias. However, the literature included in this study did not mention whether it was double-blind or allocation hiding.

In conclusion, 19 literatures were included in this study to analyze the clinical effect and safety of Yinzhihuang combined phototherapy in the treatment of neonatal pathological jaundice. The results showed that Yinzhihuang combined phototherapy was better than phototherapy in the treatment of neonatal pathological jaundice and the safety was also better than phototherapy. However, there are some limitations in these studies, such as no blinded method, no further follow-up of children, single case source and no multicenter study, etc. The clinical effect and safety of Yinzhihuang combined phototherapy in neonatal pathological jaundice treatment need to be confirmed by clinical multicenter prospective studies.

Conflict of interests:

The authors declared no conflict of interests.

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