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Recent Advances in Adjuvant Pharmacotherapy for Neonatal Indirect Hyperbilirubinemia: A Narrative Review

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Abstract

Context: Hyperbilirubinemia is a common cause for diagnostic work-up and therapeutic intervention in neonates and needs a convenient, quick, and safe treatment modality. Phototherapy is the most common treatment for neonatal jaundice; however, complementary treatment is still needed. Despite the identification of the enzymatic pathways of bilirubin catabolism, few pharmacological interventions have been found to be effective in reducing bilirubin, along with traditional phototherapy. This review was conducted to evaluate recent pharmacotherapies as adjuvants to phototherapy for the treatment of neonatal indirect hyperbilirubinemia (IHB).

Evidence Acquisition: This study was carried out through a literature search with the keywords of Infant, Newborn, and Indirect Hyperbilirubinemia, combined with Drug Therapy, in PubMed, Scopus, International Statistical Institute, Web of Science, Cochrane, and Embase databases. This study included relevant articles (i.e., randomized controlled trials, observational studies, guidelines, and reviews) written in English and published between 2012 - 2022.

Results: This narrative review first assessed the relevant articles to define IHB and its etiology. Then, the efficacy and side effects of recent pharmacologic agents as adjuvants to phototherapy were discussed. Additionally, this study reviewed the efficacy and safety of drugs prescribed to neonates to prevent jaundice.

Conclusions: The best drug for adjuvant pharmacotherapy, in addition to phototherapy, for neonatal jaundice has not still been identified. The use of probiotics, prebiotics, synbiotics, and ursodeoxycholic acid (UDCA) in adjuvant to phototherapy has been recently increasing, and beneficial results were observed in most studies. The use of agar, charcoal, fibrate, and phenobarbital had a minor therapeutic role in recent years. There were conflicting results about the efficacy of herbal agents in neonatal jaundice. The use of intravenous immunoglobulin (IVIG), metalloporphyrin, and albumin is also limited to severe or immune-related IHB cases. The prescription of the aforementioned drugs sometimes had different results. Therefore, further research in this regard is necessary.

Keywords: Infant, Newborn, Drug Therapy, Indirect Hyperbilirubinemia

1. Context

Hyperbilirubinemia is a common cause for diagnostic work-up and therapeutic intervention in neonates. The prevalence of indirect hyperbilirubinemia (IHB) in term and preterm infants varies from 60% to 90%. The excessive production of bilirubin (as a catabolic product of heme-containing molecules) or reduction of its elimination led to increasing serum bilirubin levels (1). The IHB is accompanied by an increased risk of persistent neurological complications, and timely treatment is mandatory. The main treatment modality for the past decades has been based on phototherapy. However, phototherapy has some adverse effects, such as increasing the risk of infantile cancer and changing the function of newborns' immune systems. Phototherapy also does not eliminate the need for exchange transfusion (ET) in all infants and cannot prevent bilirubin synthesis and accumulation (2-4). Despite the identification of the enzymatic pathways of bilirubin catabolism, few pharmacological interventions have been found to be effective in reducing bilirubin production or increasing its elimination (5). This review will discuss new advances in pharmacotherapy for neonatal IHB and their safety, efficacy, and side effects.

2. Evidence Acquisition and Data Sources

The current review evaluated included articles about pharmacologic modalities for preventing or treating jaundice in neonates. The reviewed articles were indepen-

dently searched by researchers from domestic databases, including IranMedex, Scientific Information Database, Magiran, IranDoc, and Medilib, and international databases, including Science Direct, PubMed, Scopus, Cochrane, Embase, Web of Science, and Medline. This study was conducted through a literature search on articles in English with the keywords of Infant, Newborn, Drug Therapy, and Hyperbilirubinemia. Randomized controlled trials (RCTs), cohort studies, systematic reviews, and narrative reviews were included in this review.

2.1. Search Strategy

(Infant [Title/Abstract]) OR (newborn [Title/Abstract]) OR (neonatal [Title/Abstract]) OR (neonate [Title/Abstract]) AND (pharmacotherapy [Title/Abstract]) OR (drug therapy [Title/Abstract]) AND (hyperbilirubinemia [Mesh]) AND (infant [Title/Abstract]) OR (newborn [Title/Abstract]) OR (neonatal [Title/Abstract]) OR (neonate [Title/Abstract]) AND (pharmacotherapy [Title/Abstract]) OR (drug therapy [Title/Abstract])

This review included the relevant articles (i.e., RCTs, observational studies, guidelines, and reviews) written in English and published between 2012 - 2022.

3. Results

This study summarized the following important issues related to pharmacotherapy in neonatal IHB:

(1) Definition of neonatal IHB

(2) Etiology of IHB in neonates

(3) Therapeutic approaches and pharmacotherapy for neonatal IHB

(4) Prophylactic pharmacotherapy in neonatal IHB

3.1. Definition of Neonatal IHB

The Bhutani nomogram was published by the American Academy of Pediatrics (AAP) and indicated the percentile curve of expected hourly total serum bilirubin (TSB) of newborns in venous blood. Significant hyperbilirubinemia in infants $\geq$ 35 weeks of gestational age (GA) is defined as a TSB > 95th percentile on the hour-specific Bhutani nomogram after birth (6, 7). Severe and extreme neonatal hyperbilirubinemia is defined as TSB > 25 and > 30 mg/dl in this GA, respectively. Prolonged hyperbilirubinemia is defined as visible jaundice beyond 2 and 3 weeks in term and preterm neonates, respectively (7). According to the latest AAP guideline, a direct serum bilirubin level > 1 mg/dL is defined as abnormal, and a direct bilirubin level of > 20% of the total is no longer accepted as a diagnosis of cholestasis (8).

3.2. Etiology of IHB in Neonates

Bilirubin is the final catabolic product of heme-containing molecules. Heme is degraded by heme oxygenase and produces biliverdin. Biliverdin is converted to unconjugated bilirubin (UCB) by biliverdin reductase and transported to the liver. Water-soluble conjugated bilirubin (CB) is produced by the action of hepatocyte uridine diphosphate-glucuronate glucuronosyltransferase 1A1 (UGT1A1) enzyme. Most of CB is reduced by intestinal bacterial flora and excreted through stool. A small amount is reabsorbed by the intestinal mucosa and returned to the blood circulation, called enterohepatic circulation (7, 9).

Benign (physiologic) neonatal IHB in the first week after birth is caused by increased red blood cell (RBC) turnover, enterohepatic circulation, and liver UGT1A1 enzyme immaturity. Overall, the imbalance between bilirubin production and its metabolism leads to IHB. Physiologic IHB often recovers spontaneously without the need for treatment. On the other hand, pathologic IHB requires medical intervention.

Breastfeeding problems are among the most important causes. Breastfeeding jaundice has two types. One is due to inadequate breastfeeding, calorie intake, and dehydration on the 2nd to 4th day after birth. Early and adequate breastfeeding can prevent this type of jaundice. Another type is breast milk jaundice due to abnormality in breast milk that occurs later (10, 11). Since indirect bilirubin is fat-soluble and can pass through the brain-blood barrier (BBB), it increases the risk of neurological deficits, such as hearing loss, intellectual development disorders, kernicterus, and even death (6). The etiology of pathological IHB varies depending on the geographical area and genetic structure of infants. The most common etiological factors are Rh and ABO and subgroups' blood incompatibilities, breastfeeding jaundice, urinary tract infections, glucose-6-phosphate dehydrogenase deficiency, and infection (10, 11).

3.3. Therapeutic Approaches and Pharmacotherapy for Neonatal IHB

Phototherapy: Phototherapy is still the gold standard therapy for the treatment of neonatal IHB; however, it might induce hyperthermia, skin rash, diarrhea, dehydration, and retinal damage (3) and does not prevent the accumulation of bilirubin and the need for ET in all cases. Considering the aforementioned problems, it is better to administer adjuvant pharmacological agents (3, 4). Despite the identification of the enzymatic pathways of bilirubin catabolism, few pharmacological interventions have been found to be effective in lowering bilirubin production or increasing its elimination (5). To date, numerous studies

and systematic reviews have been conducted in the field of adjuvant therapeutic drugs, along with phototherapy, in IHB, and this review will evaluate the aforementioned studies.

3.4. Fibrates

Fibrate, as a lipid-lowering drug, can enhance bilirubin conjugation and excretion through the induction of UGT1A1 (12). Fibrates are a class of phenoxy-isobutyric acid derivatives, which are peroxisome proliferator-activated alpha receptor agonists. Additionally, clofibrate processes the transfer of albumin-bound bilirubin to hepatocytes and induces hepatic uptake and conjugation of bilirubin (13). Numerous RCTs assessed fenofibrate as an adjuvant to phototherapy in neonates with IHB (12-16). Khafaga et al. revealed that a single dose of fenofibrate (10 mg/kg) as an adjuvant to phototherapy in neonates with hyperbilirubinemia was associated with a significant reduction of serum bilirubin levels (12). Chaudhary et al. demonstrated that fenofibrate appears to be an effective and safe drug for the treatment of neonatal IHB, consistent with the results of a previous study (15). Other studies showed that fenofibrate is well tolerated and associated with a significant reduction of the serum bilirubin level, duration of phototherapy, and hospital stay (16-19). Gholami et al. concluded that a single dose of 100 mg/kg clofibrate can decrease the serum bilirubin level compared to a control group (20). The results of a systematic review by Eghbalian et al. revealed that clofibrate could effectively reduce TSB (13). However, no statistically significant difference was observed in the bilirubin reduction rate in Prabha and Saravanan's study with a single dose of fenofibrate (10 mg/kg), despite the shorter duration of phototherapy (21).

Zamiri-Miandoab et al., in a systematic review and meta-analysis, revealed that although the results of five studies showed the significant effects of fenofibrate as adjuvant therapy on reducing the TSB level, the meta-analysis failed to show the same results in the studied groups and recommended performing further trials (22). Therefore, further studies are required to be performed.

3.5. Probiotics, Prebiotics, and Synbiotics

Probiotics are living bacteria that have beneficial effects on the host by modulating intestinal flora and increasing the immunity of the gastrointestinal tract (3, 23). Probiotics can reduce enterohepatic circulation by inhibiting beta-glucuronidase activity and reducing the degradation of CB. Additionally, the modulation of intraluminal pH, better gastrointestinal motility, and improvement in stool viscosity are among other mechanisms justifying their effects on the TSB level (3). The most common probiotic used in neonates is *Bifidobacterium* (24). Several trials have evaluated the effects of probiotics, prebiotics, and synbiotics in neonatal IHB adjunct to phototherapy. Walker-Pizarro et al., in an RCT on the efficacy of *Lactobacillus reuteri* and *Saccharomyces boulardii* in neonatal IHB, observed no statistical difference in bilirubin reduction rate consistent with the results of Afzal et al.'s study (25, 26). In this regard, Santosa et al. demonstrated no significant effects of probiotics on decreasing serum bilirubin levels (27). Mutlu et al. evaluated the effects of probiotics supplementation on neonatal IHB caused by isoimmunization alone and showed no difference in the bilirubin reduction rate in the first 24 hours of life. Mutlu et al. revealed that the effect of probiotics occurs at 36 hours of life (28). Goodarzi et al. indicated that probiotics are not effective in reducing the duration of phototherapy in term and near-term neonates (29). Deshmukh et al. mentioned in a systematic review and meta-analysis that probiotics might reduce the duration of phototherapy in icteric neonates. Deshmukh et al. did not recommend the routine use of probiotics to prevent or treat neonatal IHB (30).

On the other hand, Nouri et al. prescribed PediLact as a synbiotic in icteric term and preterm neonates > 35 weeks of GA and revealed significant differences in the rate of bilirubin reduction and duration of hospital stay in the intervention group (3). In numerous studies, the findings showed that the addition of oral probiotics/prebiotics/synbiotics to phototherapy is associated with a higher bilirubin reduction rate, reduced phototherapy duration, and shorter hospitalization (31-35). In addition, *S. boulardii*, in combination with phototherapy, was effective and safe in reducing bilirubin levels and duration of phototherapy in icteric premature infants in Hu et al.'s study (36). On the other hand, a meta-analysis by Chen et al. showed that probiotics supplementation is an effective and safe adjunctive treatment for pathological neonatal IHB (37). According to different results, the routine use of probiotics, prebiotics, and symbiotics cannot be ordered.

3.6. Herbal Agents for Treatment of Neonatal Jaundice

Herbal therapies for the treatment of neonatal hyperbilirubinemia have been recently developed. Traditional herbal medicines might play a significant role in decreasing the serum bilirubin level by increasing defecation and interrupting the enterohepatic cycle (38). *Cotoneaster* (the purgative manna), pomegranate paste, jujube, barley flour, *Alhagi maurorum Medik*, *Fumaria officinalis*, and chicory aroma are the famous herbal agents for this issue (39, 40). Pojark manna (Shir-e-Khesht) is popular in Persian medicine. Manna contains various types of carbohydrates, such as glucose and mannitol, phenolic compounds, and flavonoids. Phenolic compounds have excellent antioxidant activity, which protects hepatocytes against oxidative

stress and can decrease TSB. Additionally, it has a laxative effect that accelerates the passage of meconium (41). It is noteworthy that each milliliter of the purgative manna contains 300 mg of mannitol and is absorbed minimally from the gastrointestinal tract leading to osmotic diarrhea (42).

In Aghababaeian et al.'s study, *Cotoneaster frigidus* extract and a placebo were administered to intervention and control groups, respectively, in addition to phototherapy. The level of bilirubin was checked every 24 hours for 72 hours after the initiation of treatment. The aforementioned study showed a significant difference in TSB between the two groups at 48 and 72 hours after the initiation of treatment (43).

Monsef et al. demonstrated in a double-blinded RCT that the purgative manna, along with phototherapy, can significantly reduce the duration of hospitalization and TSB at 48 and 72 hours (42). Rezapour et al. performed a systematic review and concluded that herbal remedies (especially bilineaster) are probably effective as adjuvant therapies, along with standard therapies, in reducing the serum bilirubin level, hospitalization duration, and rehospitalization (44). A systematic review by Feng et al. showed that Yinzhihuang granules (i.e., a Chinese herbal agent consisting of extracts of *Artemisia capillaris Thunb*., *Gardenia jasminoides Ellis*, *Lonicera japonica Thunb*., and *Scutellaria baicalensis Georgi*), along with phototherapy, are more effective than phototherapy alone in reducing TSB (45).

On the other hand, Mahyar et al. conducted a study to compare the therapeutic effects of the purgative mana in addition to phototherapy, clofibrate, phototherapy, and phototherapy alone. The aforementioned study showed that prescribing the purgative manna and clofibrate had no effect on the reduction of TSB in term neonates (46). Fakhri et al. conducted a systematic review and meta-analysis and evaluated the effects of natural products on preventing neonatal jaundice and revealed no statistically significant difference (47). It should be considered that herbal therapy has very few side effects but a slow recovery time; therefore, it is not a favorite option for the treatment of neonatal icter (48).

3.7. Effect of Zinc on Hyperbilirubinemia of Newborns

Zinc sulfate, as an antioxidant and enzyme cofactor, might have a possible role in heme catabolism and bilirubin production. Zinc salts reduce the enterohepatic circulation of bilirubin and can inhibit the heme oxygenase enzyme (49, 50). Faal et al. showed that the use of 1 cc/kg/day of zinc sulfate in preterm icteric neonates (31 - 36 weeks of gestation) significantly reduced bilirubin levels within 48 hours of treatment, compared to neonates who received a placebo (51). Similar results were obtained with this method in term neonates (52). A systematic review and meta-analysis conducted by Kalvandi et al. showed that zinc sulfate is a safe and effective medication in reducing TSB (53). In a meta-analysis conducted by Yang et al. on five RCTs, zinc sulfate therapy had no effect on TSB but reduced phototherapy duration (54). Khoshnevisasl et al. did not observe a significant reduction in TSB levels and the duration of hospitalization in icteric neonates receiving 10 mg/kg/day zinc sulfate compared to a control group (49). Waheed et al. also obtained similar results with a daily dose of 10 mg/kg of zinc sulfate (55). It should be considered that there are concerns about increasing the zinc serum level during phototherapy. Therefore, the administration of zinc supplements, along with intensive phototherapy, might induce zinc toxicity and is not a suitable therapeutic option in neonates with high levels of TSB requiring intensive phototherapy (55, 56). Some studies have denied the increase in the zinc level after phototherapy (57).

3.8. Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is a United States Food and Drug Administration (FDA)-approved drug, even for neonates, commonly used to manage cholestatic hyperbilirubinemia. The UDCA enables the emulsification of bile in the biliary ducts and facilitates the excretion of bile secretion. The induction of intestinal UGT1A1 expression, reduction of absorption of bile acid from the intestine and subsequent reduction of enterohepatic circulation, and anti-apoptotic and antioxidant effects are the main mechanisms justifying the therapeutic effect of UDCA on IHB (58). Honar et al. revealed that UDCA could reduce the duration of phototherapy, the hospitalization period, and the mean TSB in the intervention group, consistent with the results of other trials (58-64). Two systematic reviews demonstrated the efficacy of UDCA in neonatal IHB (65, 66). Nevertheless, in another trial by Mirzarahimi et al., the addition of UDCA made no significant difference in comparison to phototherapy alone (67). Akefi et al. showed that despite the significant decrease in the bilirubin level at 12 and 24 hours after treatment in the UDCA-receiving group, phototherapy duration was not different in the two groups (68).

3.9. Intravenous Immunoglobulin

Although the FDA has not yet approved the use of intravenous immunoglobulin (IVIG) in neonates, it has been used in numerous trials. Alloimmune hemolytic disease (AIHD), including ABO or Rh incompatibility, is the most common indication for IVIG administration to prevent or treat severe IHB. The IVIG blocks the RBC receptors, prevents antigen-antibody interactions and hemolysis, and

subsequently decreases severe hyperbilirubinemia. Additionally, IVIG has an effect on antigen-presenting cells and Fc receptors (69). Moreover, in a systematic review performed by Louis et al., the authors concluded that IVIG is beneficial in cases of Rh incompatibility (70). El Fekey et al. concluded that the administration of IVIG, along with phototherapy, significantly reduces bilirubin levels in hemolysis, duration of phototherapy, need for ET, and hospital stay (71). According to Vardar et al.'s study, IVIG reduces the need for ET and should be considered due to its relative benefits in neonates with AIHD (72). In contrast to this finding, Al-Lawama et al. observed a higher risk of rebound IHB and the need for ET in infants who received IVIG with phototherapy (73). In a recent meta-analysis by Zwiers et al., which was performed on nine eligible studies, IVIG did not prevent the need for ET in neonates with hemolysis (74). Furthermore, Okulu et al., in an RCT, determined that one dose of IVIG did not prevent ET or decrease the duration of phototherapy in infants with hemolytic disease due to ABO incompatibility and severe IHB (75). Consistent with the results of the aforementioned study, one RCT conducted by Smits-Wintjens et al. concluded that the prophylactic prescription of IVIG could not significantly decrease the need for ET in infants with Rh incompatibility (76). In this regard, Pan et al. demonstrated no appreciable benefits from IVIG administration in neonates with ABO incompatibility (77). Different results might be due to the characteristics of specific IVIG formulations and the primary etiology of jaundice in each case (69). Due to the unclear risk-benefit ratio of using IVIG to treat immune-mediated IHB, further studies are needed to evaluate IVIG's efficacy and safety in neonates. In addition, the side effects of IVIG, including necrotizing enterocolitis, thrombosis, anaphylaxis, apnea, and cardiac arrhythmia, should be considered.

3.10. Metalloporphyrins

Metalloporphyrins can prevent neonatal IHB by inhibiting the activity of heme oxygenase (24). Only tin protoporphyrin, tin mesoporphyrin (SnMP), and zinc protoporphyrin have been used in human neonates and are in phase II clinical trials. They are not approved for routine use in some countries, such as the USA or UK. A single intramuscular injection on the first day of life might reduce the need for subsequent phototherapy in high-risk neonates (i.e., cases with ABO, Rh incompatibility, or glucose-6-phosphate dehydrogenase deficiency). Transient erythroderma after phototherapy is the main side effect of metalloporphyrins. Due to the blockade of heme metabolism and reduction of the free iron status of cells, metalloporphyrins might affect hemoproteins and other enzymes, including cytochrome P450 (78). Rosenfeld et al. concluded that SnMP combined with phototherapy was superior to phototherapy alone in neonates with significant IHB due to hemolysis (79), consistent with the results of another study (80). The efficacy, toxicity, and long-term benefits of metalloporphyrins are not clear, and further studies are needed in this regard (24, 78, 81).

3.11. Phenobarbital

Phenobarbital has been used to treat neonatal IHB since 1960. Phenobarbital increases the activity of the uridine 5′-diphosphate-glucuronic acid (UDPGT) enzyme in hepatocytes and accelerates the metabolism of bilirubin. In addition, phenobarbital can increase urinary bilirubin excretion but has a slow action time (usually three days) (24). Numerous RCTs revealed that either the administration of phenobarbital to pregnant mothers before delivery or to neonates after delivery limits the TSB level. Furthermore, phenobarbital might stimulate UDPGT activity in Crigler-Najjar syndrome type 2 (82, 83). Kaabneh et al. concluded that the oral dose of 2.5 mg/kg phenobarbital in combination with phototherapy might help newborns with isoimmune hemolytic diseases and lead to a faster decrease in TSB (84). Another study revealed that oral prophylactic and therapeutic usage of phenobarbital (3 mg/kg/day at 6 hours of life and the next 5 days) significantly reduces the peak serum bilirubin level and decreases the duration of phototherapy in very low birth weight infants (83, 85). Phenobarbital supplementation in neonates with prolonged IHB can significantly accelerate the reduction in the serum bilirubin level (82). This drug has some adverse effects, such as sedation, an increase in the risk of bleeding, and 1 - 2 weeks of action after its discontinuation (86).

3.12. Agar

Oral agar, a complex mixture of polysaccharides derived from seaweeds, is a low-cost and safe product. It binds to UCB in the gut and decreases enterohepatic circulation. Agar has been used to date for the treatment of neonatal IHB; however, the effectiveness of agar is quite conflicting and controversial. Agar decreased TSB and the length of phototherapy and hospitalization in some trials (87-89). Bahman Bijari et al. concluded that oral agar supplementation in healthy term neonates reduces the bilirubin level in the first days after birth (90).

3.13. Albumin Infusion in Neonatal Hyperbilirubinemia

The intravenous albumin injection during blue light phototherapy might induce serum bilirubin reduction by

binding to free bilirubin. Albumin is bounded by water-soluble bilirubin and produces a more stable form, prevents its reverse transformation, and increases the excretion of bilirubin. On the other hand, binding to albumin leads to an increase in the molecular weight of bilirubin, prevents its penetration into the BBB, and reduces neurotoxicity (24). Most of the studies have investigated the effect of this product in high bilirubin levels near ET. In a recent study by Magai et al., there was no significant difference in the rate of serum bilirubin reduction per hour or need for ET between the case group (who received albumin 20%) and control group (who were treated with normal saline as the placebo) (91). This result was confirmed in Chan and Schiff's study (92). The infusion of 1 g/kg of 20% albumin before ET was not superior to 0.9% saline for reducing the bilirubin level and post-ET phototherapy duration in Dash et al.'s study (93). In this regard, a meta-analysis evaluated the results of four clinical trials related to the administration of albumin 20%, along with phototherapy. The aforementioned meta-analysis determined that pre-ET albumin infusion is a safe and effective modality in reducing the necessity of ET (94). Overall, there are conflicting results about albumin. Moreover, in addition to its expensiveness, the side effects, such as the risk of volume overload and infection, should be considered (94).

3.14. Prevention Modalities for Neonatal Indirect Hyperbilirubinemia

Some trials were designed to prevent the occurrence of jaundice in neonates by prescribing medicine to healthy infants. Some of these studies are discussed in this section. Mousavinejad Chenarani et al., in a triple-blinded clinical trial, prescribed daily *Saccharomyces boulardii* for the prevention of IHB in healthy term neonates without any risk factor for five days and revealed a significant preventive effect on the occurrence of IHB in the intervention group (23). Itova and Georgieva investigated the effect of the administration of probiotics for the prevention of neonatal jaundice in full-term newborns and revealed a significant reduction in the incidence of IHB (95). In addition, probiotics lowered the serum bilirubin levels of healthy neonates significantly without any adverse reaction in Suganthi and Das's study (96). The findings of Fakhri et al. in a randomized double-blinded clinical trial showed that the consumption of the purgative manna by neonates three times a day for three days could be effective in preventing jaundice and significantly decreases the need for phototherapy and hospitalization, compared to a placebo (41). Boskabadi et al. conducted a study to evaluate the preventive effect of zinc consumption during the third trimester of pregnancy. They showed that an increased serum zinc level in both newborns and mothers could reduce the incidence and severity of IHB (97).

Chawla and Parmar showed that prophylactic phenobarbital administration for 3 - 5 days in a dose of 5 mg/kg after birth is effective in lowering serum bilirubin in neonates with hemolytic disease, extravasated blood and very low birth weight without any significant side effects (98). However, the prenatal administration of phenobarbital might affect cognitive development and is not recommended (99).

This narrative review first assessed the relevant articles to define IHB and its etiology. Then, it discussed the efficacy and side effects of recent pharmacologic agents as adjuvants to phototherapy. In addition, this study reviewed the efficacy and safety of drugs prescribed to neonates to prevent jaundice.

4. Conclusions

The best drug for adjuvant pharmacotherapy, in addition to phototherapy, for neonatal jaundice has not still been identified. The use of probiotics, prebiotics, synbiotics, and UDCA in adjuvant to phototherapy has been recently increasing, and beneficial results were observed in most studies. The use of agar, charcoal, fibrate, and phenobarbital had a minor therapeutic role in recent years. There were conflicting results about the efficacy of herbal agents in neonatal jaundice. The use of IVIG, metalloporphyrin, and albumin is also limited to severe or immune-related IHB cases. The prescription of the aforementioned drugs sometimes had different results. Therefore, further research is necessary.

4.1. Limitations

The limitations of this review included the uncertain level of evidence and grades of recommendations based on the design of the articles (grades A-D) and the limited number of cohort and trial articles.

Footnotes

Authors' Contribution: MZ conceived and designed the evaluation and drafted the manuscript. SAHN participated in designing the evaluation, collecting the data, and article searching and helped draft the manuscript. MZ and SAHN re-evaluated the data. HH and MZ revised the manuscript. All the authors read and approved the final manuscript.

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