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ROLE OF URSODEOXYCHOLIC ACID IN MANAGEMENT OF INDIRECT HYPERBILIRUBINEMIA

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Abstract:

Hyperbilirubinemia is a common newborn condition. The purpose of this study was to examine the effect of ursodeoxycholic acid (UDCA) on infants with indirect hyperbilirubinemia.

In neonates with indirect hyperbilirubinemia, ursodeoxycholic acid had additive effects with phototherapy. Ursodeoxycholic acid could be considered as a novel adjuvant therapy for neonatal indirect hyperbilirubinemia in order to decrease the mean total serum bilirubin and shorten the duration of phototherapy. *Hyperbilirubinemia is a common newborn condition. The purpose of this study was to examine the effect of ursodeoxycholic acid (UDCA) on infants with indirect hyperbilirubinemia.*

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Hyperbilirubinemia is a common new-born condition. The purpose of this study was to examine the effect of ursodeoxycholic acid (UDCA) on infants with indirect hyperbilirubinemia. We have conducted a narrative review through electronic databases; PUBMED, EMBASE, for all relevant studies that were published up to 2022. In neonates with indirect hyperbilirubinemia, ursodeoxycholic acid had additive effects with phototherapy. Ursodeoxycholic acid could be considered as a novel adjuvant therapy for neonatal indirect hyperbilirubinemia in order to decrease the mean total serum bilirubin and shorten the duration of phototherapy.

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INTRODUCTION:

Approximately fifty percent of term neonates and eighty percent of preterm neonates are diagnosed with hyperbilirubinemia. Approximately 10% of infants have elevated bilirubin levels at one month of age [1, 2]. Between 5% and 15% of neonates require close observation and phototherapy, which is typically initiated 2–5 days after birth [1, 3]. Phototherapy is used to prevent neurotoxicity caused by unconjugated free bilirubin that crosses the blood-brain barrier when the serum total bilirubin level is rapidly increasing or high [4].

Phototherapy has remained the standard treatment for neonatal hyperbilirubinemia since its introduction 60 years ago [5]. If bilirubin levels continue to rise despite phototherapy, severe hyperbilirubinemia may require exchange transfusion. Phototherapy sessions typically last between 12 and 48 hours [6]. In addition to prolonged hospitalization, common side effects of phototherapy include erythematous rash, retinal damage, irritability, loose stools, dehydration, feeding difficulties, and "bronze-baby syndrome" [7]. Recent discussions have focused on the potential long-term risks of neonatal phototherapy, as phototherapy has been linked to slightly increased rates of infant and childhood cancer, the number of melanocyte nevi, and epileptic convulsions during childhood [9].

There is increased interest in potential pharmacological therapies for unconjugated hyperbilirubinemia, both to shorten hospital stays and to avoid more intensive therapies and their harmful side effects, such as those seen with exchange transfusions. Few studies have evaluated the efficacy of ursodeoxycholic acid (UDCA) as an adjuvant therapy [9]. It has been hypothesized that UDCA, a bile acid, works by preventing the reabsorption of bilirubin from the intestines and thus occupying enterohepatic circulation. Although UDCA is an unapproved treatment for neonates, it is widely used for conjugated hyperbilirubinemia and liver disorders [10, 11]. In general, UDCA is well tolerated [11]. It has been reported that UDCA is effective at reducing the duration of phototherapy in term healthy neonates, neonates with illness, and neonates with G6PD deficiency [9]. A previous study found that combining UDCA with standard phototherapy had no added benefit [12].

DISCSSION:

A study by Cuperus et al. [13] could shed light on the role of UDCA in UCB reduction. During indirect hyperbilirubinemia, the investigation revealed that UDCA treatment captured UCB that was excreted to the intestinal lumen via direct diffusion. Several factors reduced the effectiveness of UCB's direct diffusion into the intestinal lumen. First, newborns lack enough intestinal anaerobic bacteria, despite the fact that these floras could reduce the amount of UCB entering the enterohepatic circulation by converting it to urobilinoids. Second, the immaturity of the neonatal liver and intestines may result in a delayed elimination of bilirubin. The UCB load is also augmented by -glucuronidase activity in breast milk, which converts intestine direct bilirubin back to UCB [14,15]. The administration of UDCA could prevent UCB from entering the enterohepatic circulation and increase its elimination through feces (**Fig. 1**) [16].

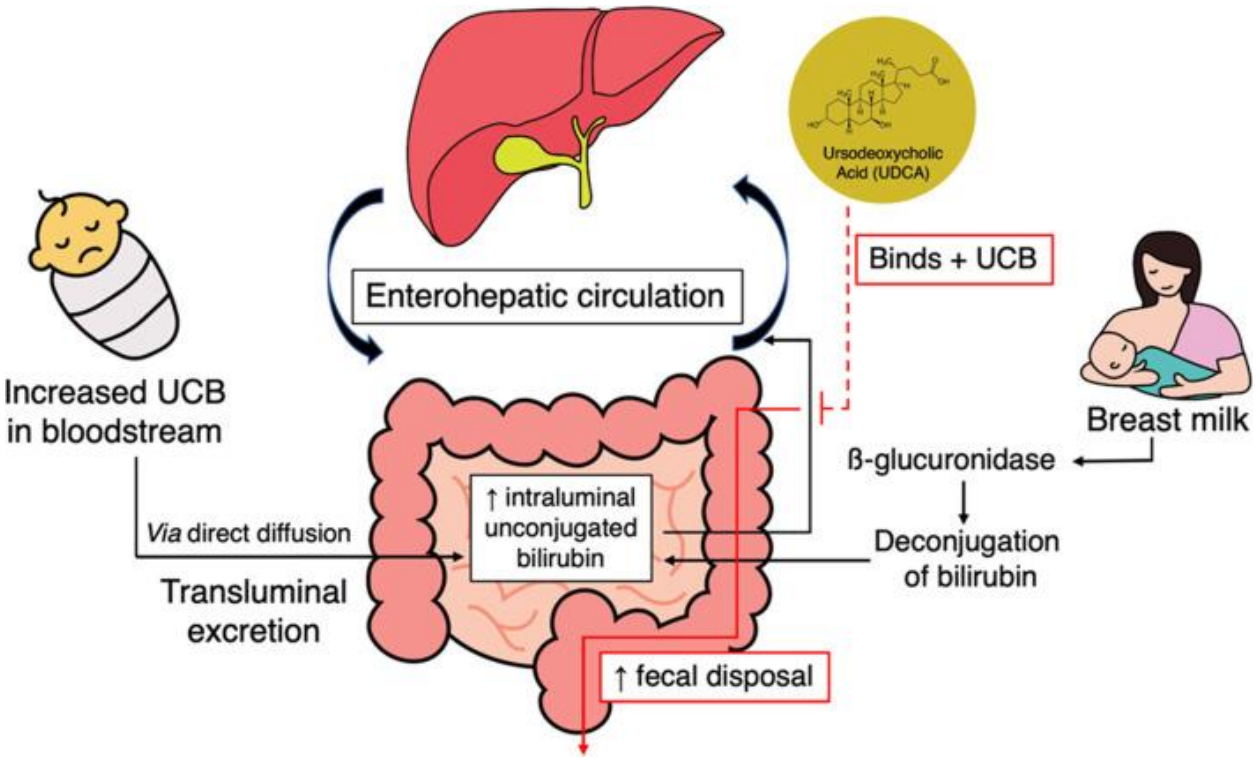

Fig. 1: Role of ursodeoxycholic acid (UDCA) in indirect hyperbilirubinemia. UCB = unconjugated bilirubin; red lines = UDCA mechanism of action [16]

In neonatal indirect hyperbilirubinemia, novel adjuvant treatments are required to promote bilirubin clearance, decrease phototherapy duration, and decrease exchange transfusion rate. Studies have demonstrated that baby massage, intravenous fluid supplementation, and several agents such as fenofibrate and zinc sulfate can help ameliorate neonatal hyperbilirubinemia [17]. However, some of these options are not helpful in the acute phase because they require four days to show benefit on bilirubin concentration or had no significant impact on phototherapy duration [17]. Ursodeoxycholic acid (UDCA), also known as ursodiol, is a bile acid that is frequently used to treat cholestatic liver disease [18]. UDCA enhances endogenous bile secretion, displaces more harmful components of endogenous bile acids, and decreases enterohepatic circulation. Through its anti-apoptotic, anti-inflammatory, and antioxidant activities, UDCA also exerts neuroprotective and hepatoprotective characteristics [19]. Also examined is UDCA's potential function in indirect hyperbilirubinemia. Randomized clinical research conducted by Honar et al. found that UDCA could shorten the length of phototherapy and hospitalization, and that the intervention group's mean bilirubin levels were considerably lower than those of the control group. Another study by Mirzarahimi et al. [20] demonstrated that the inclusion of UDCA did not provide a substantial advantage over phototherapy alone.

Activated charcoal, D-penicillamine, phenobarbital, metalloporphyrin, clofibrate, and bile salts have been used to treat indirect hyperbilirubinemia [21] to date. Several investigations have demonstrated that phenobarbital is helpful at reducing indirect hyperbilirubinemia and decreasing phototherapy time [22]. Nonetheless, it has side effects such as increased sleepiness, decreased breast-feeding, dehydration, and neurological issues.

Ursodeoxycholic acid (UDCA), on the other hand, is a bile acid commonly used to treat cholestatic liver problems. It protects the liver from oxidative stress, reduces cell death, increases bile flow, and lowers immunological processes' confusing factors [23]. In children, UDCA is well tolerated and has few side effects [24].

A study on the effect of UDCA and phototherapy on unconjugated bilirubin (UCB) in rats revealed that UDCA accelerated the turnover of UCB by fecal disposal [25].

In one study, there was no significant difference between the sexes of the two groups. The majority of

patients in the trial were 3 days old (52% in the case group and 70% in the control group). This is consistent with previous research on the subject [26]. UDCA is frequently utilized to treat cholestatic liver disorders. Previous research revealed that UDCA has three major mechanisms of action: first, changes in the composition of mixed phospholipid-rich micelles, reduction of bile acid cytotoxicity of bile, and, possibly, reduction of the hydrophobic bile acid concentration in the cholangiocytes could protect cholangiocytes from the cytotoxicity of hydrophobic bile acids; second, stimulation of hepatobiliary secretion, via Ca2+-dependent mechanisms and protein Ursobil resulted to a 24-hour reduction in the duration of phototherapy in newborns with indirect hyperbilirubinemia, most likely through boosting unconjugated bilirubin turnover through its fecal disposal [27], as determined by the results of the present investigation. The only study on the effect of UDCA on lowering UCB was conducted on rats by Cuperus et al [13] in 2009; the results showed that UDCA increased UCB turnover by increasing its fecal disposal. The reduction of UCB seen in the present study appears to be caused by the same mechanism.

The decrease in total bilirubin during the first 24 hours of treatment and the 20-hour reduction in the total period of phototherapy have the potential to be clinically important and advantageous for patients. These decreases would presumably reduce the incidence of acute and long-term adverse effects and harms associated with phototherapy [17]. The shorter hospital stay may reduce expenditures associated with newborn hyperbilirubinemia and permit the reallocation of healthcare resources. Previous studies have indicated that neonates requiring phototherapy had worse nursing difficulties [28,29]. It might be hypothesized that shorter phototherapy and hospital stays may contribute to an increase in breastfeeding rates. This could offer value to these neonates [30], but this issue was not explored in the original research. There are no previous meta-analyses on this topic, thus our findings cannot be compared to those of other studies.

Two of the studies utilized a daily dose of 15 mg/kg, while four used a daily dose of 10 mg/kg, leaving the optimal dose of UDCA uncertain. We did not do a subgroup analysis based on the various doses because it was not predetermined. We discovered that experiments utilizing larger doses of UDCA yielded comparable results to those using lower dosages. As the majority of studies included in this meta-analysis did not reveal side effects [28,30], the optimal dose with the highest benefit-to-harm ratio has yet to be found.

In a prior study, it was noted that after 12 hours of therapy, the intervention group experienced a greater drop in total bilirubin than the control group. In infants with unconjugated hyperbilirubinemia, the treatment of UDCA led to a significant reduction in total serum bilirubin levels 48 hours later as well. According to the findings of Honar et al. [31], the administration of UDCA considerably reduced total bilirubin levels 12, 24, and 48 h after treatment beginning, as compared to the control group. Similar findings were observed by Hassan et al. [32] in their investigation. The results of the current study are consistent with those of earlier research. UDCA promotes biliary production of unconjugated bilirubin and lowers conjugated hyperbilirubinoma in rats, which may have led to a drop in total bilirubin level in these investigations [13].

CONCLUSION:

It can be concluded that the addition of UDCA to phototherapy in newborns with indirect hyperbilirubinemia improves the efficacy of treatment compared to phototherapy alone. The combination of UDCA with phototherapy increases TSB reduction, but this effect is clinically irrelevant because it does not reduce phototherapy and hospital stay duration. Therefore, this study does not support the clinical application of UDCA. UDCA is beneficial as an adjunct to phototherapy in the treatment of neonatal hyperbilirubinemia. The fact that UDCA reduces phototherapy duration by approximately 20 hours is clinically important and would benefit patients and their families. During the first twenty-four hours, bilirubin levels declined more rapidly than average. Before the use of UDCA may be regarded a viable option for the conventional treatment of neonatal hyperbilirubinemia, pharmacological, cost-effectiveness, and safety studies must be conducted in a variety of geographic regions using double-blinding and placebo-control.

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