“EFFECT OF URSODEOXYCHOLIC ACID IN UNCONJUGATED HYPERBILIRUBINEMIA IN THE TERM NEONATES TREATED WITH PHOTOTHERAPY.”

By

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In Partial fulfilment of requirements for the degree of

MASTER OF MEDICINE

In

PAEDIATRICS

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ABBREVIATIONS

S. No.	Abbreviation	Full Form
1	UDCA	Ursodeoxycholic Acid
2	PT	Phototherapy
3	UCHB	Unconjugated Hyperbilirubinemia
4	TSB	Total Serum Bilirubin
5	UCB	Unconjugated Bilirubin
6	NICU	Neonatal Intensive Care Unit
7	ABE	Acute Bilirubin Encephalopathy
8	BIND	Bilirubin-Induced Neurologic Dysfunction
9	LED	Light Emitting Diode
10	NVD	Normal Vaginal Delivery
11	LSCS	Lower Segment Caesarean Section
12	APGAR	Appearance, Pulse, Grimace, Activity, Respiration
13	G6PD	Glucose-6-Phosphate Dehydrogenase
14	Hb	Hemoglobin
15	UGT1A1	Uridine Diphosphate-Glucuronosyltransferase 1A1
16	RES	Reticuloendothelial System
17	ET	Exchange Transfusion
18	BSEP	Bile Salt Export Pump
19	MRP2	Multidrug Resistance-associated Protein 2
20	SPSS	Statistical Package for the Social Sciences

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ABSTRACT

Background

Neonatal hyperbilirubinemia affects 60-80% of term neonates in the first week of life, with phototherapy (PT) being the standard treatment. However, prolonged PT has limitations, leading to the exploration of adjuvant therapies such as Ursodeoxycholic Acid (UDCA) to enhance bilirubin clearance.

Objective

To evaluate the efficacy and safety of UDCA as an adjunct to PT in term neonates with unconjugated hyperbilirubinemia (UCHB) by comparing bilirubin reduction, phototherapy duration, and hospital stay between neonates receiving UDCA + PT versus PT alone.

Methods

A randomized controlled study was conducted on 100 term neonates, divided into:

- Group 1 (UDCA + PT, n = 50) receiving oral UDCA (10–15 mg/kg/day) with PT.
- Group 2 (PT-only, n = 50) receiving standard PT alone.

Total serum bilirubin (TSB) levels were measured at admission, 24 hours, and 48 hours. Phototherapy duration, NICU stay, and adverse effects were analyzed. Statistical analysis was performed using SPSS software, with $p < 0.05$ considered significant.

Results

The baseline characteristics were comparable between both groups ($p > 0.05$). The TSB decline at 48 hours was 9.3 ± 1.75 mg/dL in the UDCA + PT group versus 9.8 ± 1.9 mg/dL in the PT-only group ($p = 0.175$). The mean phototherapy duration was 47.84 ± 2.5 hours in the UDCA group and 48.22 ± 5.5 hours in the control group ($p = 0.66$). The mean NICU stay was 3.02 ± 0.24 days in the UDCA group and 3.0 ± 0.2 days in the PT-only group ($p = 0.651$).UDCA was well tolerated,

with only 3 neonates experiencing mild vomiting, and no cases of diarrhea or metabolic disturbances reported.

Conclusion

UDCA may modestly enhance bilirubin clearance, but the observed differences in bilirubin reduction, phototherapy duration, and NICU stay were not statistically significant. Given its favorable safety profile, further large-scale randomized controlled trials (RCTs) are needed to confirm UDCA's role as a routine adjunct in neonates.

INTRODUCTION

Neonatal **unconjugated hyperbilirubinemia (UH)** is a widespread condition affecting approximately **60-80% of term neonates** and an even higher percentage of **preterm infants** during the first week of life[1]. The accumulation of **unconjugated bilirubin (UCB)** in the bloodstream leads to **jaundice**, which manifests as a yellow discolouration of the skin and sclerae. While neonatal jaundice is often **physiological** and self-resolving, it can progress to **severe hyperbilirubinemia (TSB > 20 mg/dL)**, increasing the risk of **acute bilirubin encephalopathy (ABE)** and **kernicterus**, both of which can cause **irreversible neurological damage**[2]. Given these risks, **timely and effective management** of hyperbilirubinemia is critical to preventing long-term complications.

The pathophysiology of **neonatal jaundice** involves several mechanisms. First, newborns experience **increased bilirubin production** due to the **shorter lifespan of fetal erythrocytes** (70-90 days, compared to 120 days in adults)[3]. Additionally, the neonatal liver has **immature conjugation abilities** due to the **low activity of uridine diphosphate-glucuronosyltransferase (UGT1A1)**, the enzyme responsible for bilirubin conjugation[4] . Furthermore, **increased enterohepatic circulation** due to high levels of **β-glucuronidase in the neonatal gut** facilitates the **reabsorption of bilirubin**, leading to prolonged jaundice[5] . While most cases of neonatal hyperbilirubinemia resolve spontaneously, some neonates develop **severe hyperbilirubinemia** requiring medical intervention.

The **American Academy of Pediatrics (AAP)** recommends **phototherapy (PT) as the primary treatment** for neonatal UH[6] . Phototherapy effectively lowers **serum bilirubin levels** by converting **UCB into water-soluble isomers**, which are excreted via **bile and urine**. Despite its

effectiveness, **prolonged PT** is associated with several complications, including **dehydration, electrolyte imbalances, thermal instability, retinal damage, oxidative stress, and disruption of maternal-infant bonding**[7] . In severe cases, **exchange transfusion** is required, but this procedure carries significant risks such as hemodynamic instability, infections, thrombocytopenia, and necrotizing enterocolitis (NEC)[8] . These limitations have prompted researchers to explore **adjuvant therapies** that could enhance bilirubin clearance and **reduce the duration of phototherapy**.

Historical aspect:

Over the years, various pharmacological agents have been investigated for managing neonatal hyperbilirubinemia. **Phenobarbital**, an enzyme inducer, has been used to enhance bilirubin conjugation but is associated with **neurological side effects** like **sedation**[9] . **Clofibrate**, a peroxisome proliferator-activated receptor (PPAR) agonist, has been shown to increase bilirubin conjugation, but its **long-term safety in neonates remains unclear**[10] . **D-penicillamine**, a metal chelator that binds bilirubin, has shown **limited efficacy**[11]. **Probiotics** have also been studied for their role in reducing **enterohepatic bilirubin recycling**, but **their effect on hyperbilirubinemia remains inconclusive**[12].

Given these challenges, **Ursodeoxycholic Acid (UDCA)** has emerged as a promising **adjuvant therapy** for neonatal UH. UDCA is a **hydrophilic bile acid** widely used in treating **cholestatic liver diseases and primary biliary cholangitis**[13]. It is hypothesized to **enhance bilirubin clearance** through multiple mechanisms. UDCA increases **hepatic bile acid transporters** such as **BSEP (bile salt export pump) and MRP2 (multidrug resistance-associated protein 2)**, thereby promoting **biliary excretion of bilirubin**[14] . Additionally, UDCA **reduces enterohepatic**

circulation by binding to bile acids, **preventing bilirubin reabsorption** in the gut[15] . It also has **anti-inflammatory and antioxidant properties**, protecting hepatocytes from **oxidative damage due to bilirubin overload**[16] .

Animal studies have provided strong mechanistic evidence supporting the use of UDCA in neonatal hyperbilirubinemia. A study by **Cuperus et al. (2009)** in **Gunn rats**, a model for **Crigler-Najjar syndrome**, demonstrated that UDCA **accelerated bilirubin metabolism** and enhanced **fecal bilirubin excretion**[17] . Similarly, **Mendez et al. (1998)** observed that UDCA facilitated **enterohepatic cycling of bilirubin** in rodents, suggesting a potential **increase in bilirubin turnover**[8] . However, despite promising **preclinical data**, human clinical evidence remains **limited and inconclusive**.

Several clinical studies have investigated the efficacy of UDCA in neonatal jaundice. A **randomized controlled trial (RCT) by Bhardwaj et al. (2020)** on **100 term neonates** (TSB levels of **13-20 mg/dL**) found that neonates receiving **UDCA with PT had a significantly faster bilirubin decline** than those on PT alone (**TSB at 24 hours of PT: 11.78 mg/dL vs. 12.47 mg/dL, respectively**)[19] . Another study by **Honar et al. (2016)** demonstrated that UDCA administration **shortened phototherapy duration by 24 hours**, suggesting its effectiveness as an **adjuvant the9rapy**[20] . Similarly, **Hasan et al. (2015)** reported a **significant reduction in TSB levels and phototherapy duration** with **no adverse effects**, further supporting UDCA's potential role in **neonatal hyperbilirubinemia management**[21]. But some studies like Maduka Donatus et al.(2019) have found **no significant advantage of UDCA+PT over phototherapy alone**[31].Further research to establish **optimal dosing, timing, and long-term safety**, are required before UDCA can be advocated as adjuvant to PT.

Given the **limitations and side effects of phototherapy**, the potential **adverse effects of prolonged bilirubin exposure**, and the **economic burden of prolonged hospital stays**, an **effective, safe, and accessible adjuvant therapy is needed**. UDCA, with its **bile acid-modulating properties**, offers a **potentially cost-effective and non-invasive** approach to enhancing bilirubin clearance. However, due to the **lack of large-scale trials or review articles ,and some conflicting results**, further studies are essential to evaluate its efficacy and safety in neonates with **unconjugated hyperbilirubinemia**(UCHB)

Our present study aims to **assess the role of UDCA in term neonates with UCHB receiving PT** and determine whether **UDCA reduces phototherapy duration, lowers peak bilirubin levels rapidly and more effectively, and decreases hospitalization duration**. This study becomes particularly significant in **resource-limited settings**, where access to **advanced phototherapy equipment and exchange transfusion facilities** may be restricted. By providing **scientific evidence on the effectiveness of UDCA**, this study could contribute to **developing improved guidelines for managing neonatal hyperbilirubinemia ,say starting UDCA along with PT** and **reducing the burden on healthcare systems**.

AIM AND OBJECTIVES

AIM:

To assess the role of ursodeoxycholic acid (UDCA) as an adjuvant to phototherapy in reducing unconjugated hyperbilirubinemia.

OBJECTIVES

To evaluate the effect of ursodeoxycholic acid

1.Reducing unconjugated bilirubin levels

2.Duration of phototherapy of infants undergoing phototherapy for neonatal hyperbilirubinemia.

REVIEW OF LITERATURE

Neonatal jaundice is one of the most frequently encountered conditions in neonatology, affecting nearly 60% of term neonates and 80% of preterm neonates within the first week of life[1]. is primarily caused by **unconjugated hyperbilirubinemia** due to immature liver function and increased breakdown of fetal erythrocytes.

While mild jaundice usually doesn't require any intervention,but severe cases pose a risk of neurotoxicity,such as kernicterus**.PT** is the standard treatment,but has its limitations like dehydration,retinal damage and oxidative stress.

Recent studies suggest that **UDCA,** a bile acid,could be an effective adjuvant therapy by enhancing bilirubin clearance,reducing duration of phototherapy and improving outcomes,though results are still inconclusive.

1. Physiology of Bilirubin Metabolism:

Bilirubin metabolism is a complex physiological process that involves the breakdown of red blood cells (RBCs), hepatic conjugation, and excretion via the biliary and renal systems. The life span of RBCs is approximately **120 days**, after which they undergo degradation in the **reticuloendothelial system (RES)** of the **liver and spleen**. During this process, hemoglobin (Hb) is broken down into its components: **iron, proto-porphyrins, and protein globin chains**. The iron is recycled for new hemoglobin synthesis, while the globin chains are broken down into amino acids for reuse. The proto-porphyrins undergo further degradation to form **bilirubin**, which is an insoluble pigment and requires transport to the liver for further processing.

Unconjugated bilirubin (UCB), which is **lipophilic and water-insoluble**, binds to **albumin** in the bloodstream to facilitate its transport to the **liver**.(4- 5mg bilirubin bind to 1 gm of Albumen) The liver plays a crucial role in bilirubin metabolism, where hepatocytes **conjugate bilirubin with glucuronic acid** through the enzyme **UDP-glucuronosyltransferase (UGT1A1)**. This transformation results in the formation of **conjugated bilirubin**, which is **water-soluble** and can be excreted efficiently. The conjugated bilirubin is subsequently transported via the **bile ducts** into the **small intestine**, where it undergoes further metabolism.Within the intestines, conjugated bilirubin is converted into **urobilinogen** by bacterial enzymes. Some of the urobilinogen is **reabsorbed into the enterohepatic circulation**, returning to the liver for re-excretion, while the majority is oxidized into **stercobilin**, which is excreted in feces and gives stool its characteristic **brown color**. A small fraction of urobilinogen is also absorbed into the **systemic circulation**, filtered by the **kidneys**, and excreted in **urine as urobilinogen**, contributing to the yellow pigmentation of urine.

Disruptions in bilirubin metabolism can lead to pathological conditions such as **hyperbilirubinemia, jaundice**. Liver diseases like **hepatitis,** impair bilirubin conjugation, leading to an accumulation of **unconjugated bilirubin** in the bloodstream, along with increased conjugated bilirubin(>20% of total bilirubin) . Additionally, **biliary obstruction ,** prevent the excretion of **conjugated bilirubin**, causing its build-up in the blood and subsequent excretion in urine. These pathological conditions result in **jaundice**, a condition

characterized by yellow discoloration of the skin and sclera due to elevated bilirubin levels, and orange yellow or dark yellow urine while voiding itself.

Any disturbance in these pathways can lead to **clinically significant hyperbilirubinemia**, necessitating timely medical intervention.

2. Pathophysiology of Neonatal Jaundice

Neonatal jaundice occurs due to an imbalance between **bilirubin production, hepatic conjugation, and excretion**. The primary pathological mechanisms involve **increased bilirubin production, decreased hepatic clearance, and increased enterohepatic recirculation**.

1. Increased Bilirubin Production

- Neonates have a **higher RBCs turnover rate** due to a **shorter lifespan of fetal red blood cells (RBCs)** [1].
- Increased **hemolysis** occurs in conditions such as **ABO/Rh incompatibility, G6PD deficiency, and hereditary spherocytosis**, leading to excessive **unconjugated bilirubin (UCB) production** [2].
- **Inefficient hepatic uptake**: The immaturity of hepatocyte membrane carriers leads to slower bilirubin transport into liver cells, further exacerbating hyperbilirubinemia [3].

2. Decreased Hepatic Clearance

- The neonatal liver has **reduced UGT1A1 activity**, the enzyme responsible for bilirubin conjugation [4].

- This results in **delayed conversion of lipophilic UCB to hydrophilic conjugated bilirubin**, prolonging bilirubin circulation in the bloodstream [5].
- **Premature infants** have even lower enzyme activity, significantly increasing their risk for jaundice [6].

3. Increased Enterohepatic Circulation

- The neonatal intestine has **low levels of gut microbiota**, reducing the conversion of conjugated bilirubin to stercobilin and urobilin [7].
- **β-glucuronidase activity** in the neonatal gut deconjugates bilirubin, allowing it to be **reabsorbed into the bloodstream**, thereby prolonging jaundice [8].
- Breastfeeding-associated jaundice is attributed to **enhanced enterohepatic recirculation**, often seen in **breastfeeding infants with inadequate milk intake**, leading to a delay in bilirubin elimination [9].

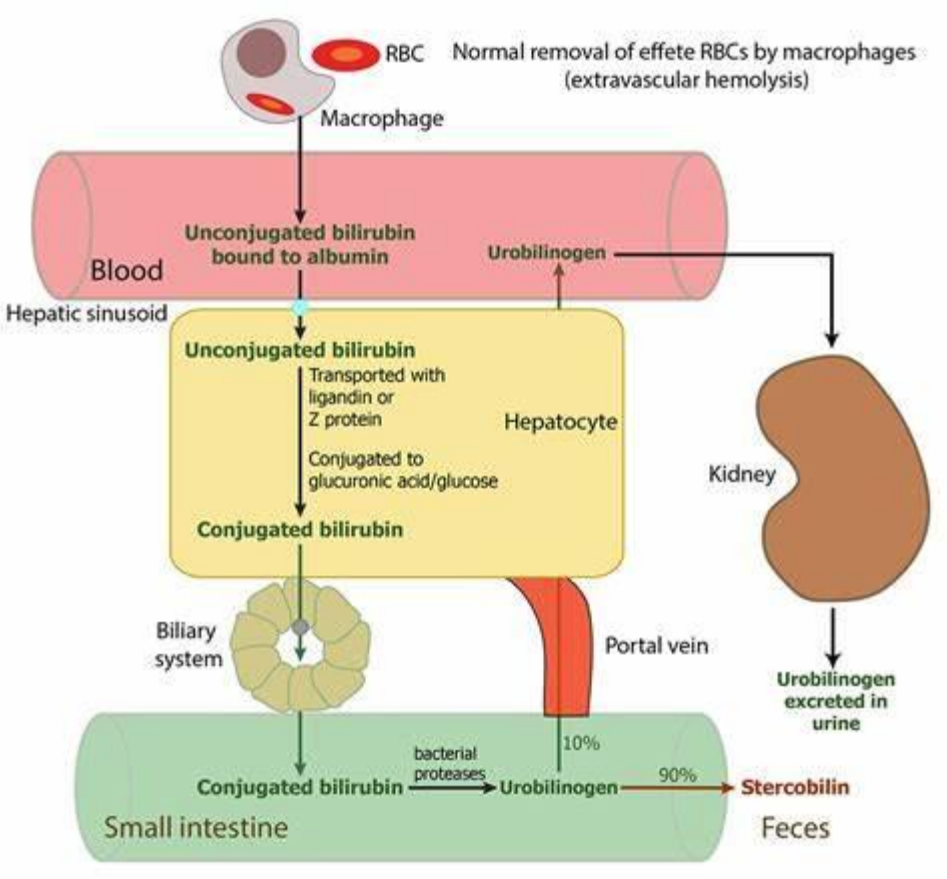


Fig.2: Pathophysiology of bilirubin metabolism (Tsai MT et al .2018) [41]

Complications of Severe Hyperbilirubinemia

If left untreated, **excessive bilirubin crosses the blood-brain barrier**, leading to **bilirubin encephalopathy (kernicterus)**, a life-threatening neurological condition.

1. *Early Signs (Acute Phase)*
2. ***Lethargy, poor feeding, and hypotonia*** *(low muscle tone)* [10].
3. ***High-pitched cry*** *and irritability* [11].
4. ***Opisthotonus*** *(abnormal posturing with arching of the back)* [12].

2. Advanced Neurological Symptoms

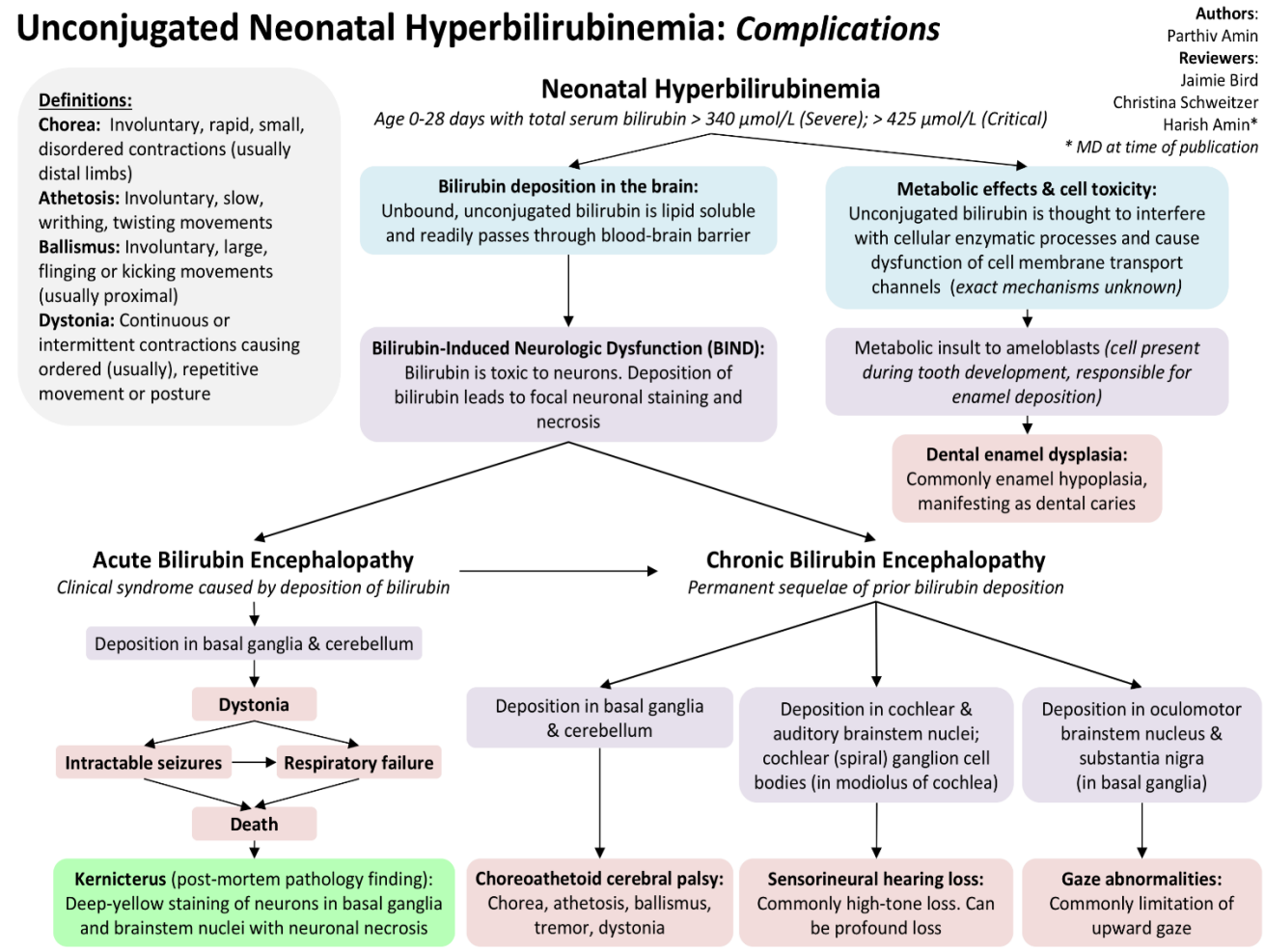
- **Seizures, apnea, and fever** [13].
- **Hearing impairment and developmental delay** [14].
- **Cerebral palsy and long-term cognitive deficits** [15].

Long-Term Consequences of Untreated Severe Jaundice

- **Choreoathetoid cerebral palsy**: A movement disorder caused by **bilirubin-induced neuronal damage(BIND)** [16].
- **Hearing impairment and speech deficits** [2].
- **Gaze abnormalities** due to **oculomotor dysfunction** [12].
- **Cognitive and learning disabilities**, impacting school performance [4].

Early detection and appropriate management are crucial to prevent bilirubin toxicity and long-term neurological damage. While **phototherapy** remains the standard treatment, recent research has focused on **adjuvant therapies** such as **UDCA**, which may enhance bilirubin clearance and minimize complications[16].

Future studies should aim at establishing evidence-based guidelines for the **safe and effective use of UDCA** , and other adjuvants in neonatal jaundice management.



15. **Fig.3:** Complications of Unconjugated Neonatal Hyperbilirubinemia and Bilirubin-Induced Neurologic Dysfunction (BIND) (**Amin P.** 18) [42]

3. Standard Treatment of Neonatal Hyperbilirubinemia

Neonatal hyperbilirubinemia requires prompt and effective management to prevent **bilirubin toxicity** and long-term **neurological complications** such as **kernicterus**. The **primary goal** of treatment is to **reduce serum bilirubin to safe levels** and prevent its accumulation in the **central nervous system (CNS)**. The two therapeutic approaches include **phototherapy (PT)** and **exchange transfusion**, both of which have been extensively studied and utilized in clinical settings.

3.1 Phototherapy

Phototherapy (PT) is the **first-line treatment** for neonatal hyperbilirubinemia. It **facilitates the conversion** of **unconjugated bilirubin (UCB)** into **water-soluble photo-isomers**, which are **easily excreted via urine and bile** without requiring hepatic conjugation [1].

Mechanism of Action

Phototherapy exerts its effect through three primary pathways [2]:

- **Photo-oxidation:** Exposure to high-intensity blue light (wavelength 460–490 nm) oxidizes bilirubin to more **polar compounds**, facilitating excretion.
- **Structural Isomerization:** UCB is converted to **lumirubin**, a water-soluble form that bypasses hepatic metabolism and is rapidly excreted.
- **Configurational Isomerization:** Changes in the molecular configuration of bilirubin increase its solubility and allow direct elimination.

Types of Phototherapy

1. **Conventional Phototherapy:** Uses **fluorescent, CFL or LED lights(SS/DS)** to provide continuous exposure.
2. **Intensive Phototherapy:** High-intensity **blue LED light** exposure, which accelerates bilirubin degradation.
3. **Fiber-Optic Phototherapy (Bili Blanket):** Uses **fiber-optic cables** placed in contact with the neonate's skin, reducing the risk of **thermal stress** and **dehydration** [3].

Clinical Efficacy

Studies have shown that **intensive phototherapy** significantly reduces **total serum bilirubin (TSB) levels**(3-4 mg/dl)in 24 hours, with a faster decline in **preterm neonates** [4]. The **American Academy of Pediatrics (AAP) guidelines** recommend **early initiation of phototherapy** based on bilirubin levels relative to postnatal age and risk factors [1].

Adverse Effects of Phototherapy

Despite its **efficacy**, phototherapy is associated with **potential complications** [5]:

- **Bronze Baby Syndrome:** Occurs due to **bilirubin photoproducts accumulating in the skin**, resulting in **grayish-brown skin discoloration**, particularly in neonates with **cholestasis**.
- **Dehydration and Electrolyte Imbalance:** Increased **insensible water loss** necessitates **adequate hydration** during treatment.

- **Retinal Damage and Oxidative Stress:** Prolonged exposure to high-intensity light may induce **oxidative injury** to **retinal cells**, requiring **eye protection** [6].
- **Interruption of Mother-Infant Bonding:** Continuous phototherapy often requires **separation from the mother**, affecting early **breastfeeding initiation** and **bonding**.

Strategies to Enhance Phototherapy Efficiency

1. **Maximizing Surface Area Exposure:** Positioning the neonate to ensure **maximum skin exposure** to the light source.
2. **Higher Spectral Intensity:** Using **LED-based phototherapy units** that provide **narrow-band blue light** in the 460–490 nm range [7].
3. **Adjunctive Pharmacotherapy:** Recent studies have explored the use of **ursodeoxycholic acid (UDCA)** as a **synergistic agent** to phototherapy, promoting faster bilirubin clearance [8].

3.2 Exchange Transfusion

Exchange transfusion (ET) is a **second-line therapy**, reserved for neonates with **severe hyperbilirubinemia** who fail to respond to **intensive phototherapy** or are at risk of developing **acute bilirubin encephalopathy** [9].

Indications for Exchange Transfusion

According to **AAP guidelines**, ET is indicated in neonates with [1]:

- **TSB levels exceeding exchange threshold values** relative to age and risk factors.

- **Failure of phototherapy** to reduce bilirubin levels effectively.
- **Signs of acute bilirubin toxicity** (lethargy, hypotonia, poor feeding, seizures).

Procedure and Mechanism

- ET involves the **removal of bilirubin-laden blood** and its **replacement with donor blood**, effectively reducing TSB and preventing **CNS deposition** of bilirubin [4].
- Typically performed via **umbilical vein catheterization**, where **small aliquots of blood** (5–10 mL/kg) are exchanged to prevent **hemodynamic instability**.

Risks and Complications of Exchange Transfusion

While effective, ET is associated with **higher risks compared to** [10]:

- **Infections and Sepsis:** Increased risk of **nosocomial infections** due to **repeated catheterization**.
- **Thrombocytopenia:** Loss of **platelets** during transfusion, necessitating platelet support.
- **Hypocalcemia and Metabolic Derangements:** Citrate in transfused blood **binds calcium**, leading to **hypocalcemia**, which may cause **cardiac arrhythmias**.
- **Hemodynamic Instability:** Large-volume **blood exchange** can cause **fluctuations in blood pressure** and **anemia**.

1. **Minimizing ET through Early Phototherapy**: Studies suggest that **aggressive phototherapy initiation** reduces the need for ET [3].
2. **Partial Exchange Transfusion:** Used in preterm neonates to **gradually** lower bilirubin levels without significant hemodynamic compromise.
3. **Adjunctive Therapy with Antioxidants:** Research suggests that **N-acetylcysteine** and **UDCA** may help **reduce bilirubin-induced oxidative stress**, thus lowering the need for ET [7].

4. Role of UDCA in Neonatal Jaundice

Neonatal jaundice is a prevalent condition, primarily caused by **unconjugated hyperbilirubinemia (UCB)**, which can lead to **bilirubin neurotoxicity and kernicterus** if not effectively managed. While **phototherapy (PT)** remains the primary treatment, certain limitations, such as **prolonged hospital stays, dehydration, and feeding difficulties**, have led to research on **adjunctive pharmacological therapies** to enhance bilirubin clearance. **Ursodeoxycholic acid (UDCA)**, a **hydrophilic bile acid**, has emerged as a promising therapeutic agent due to its **choleretic, hepatoprotective, and anti-inflammatory properties** [1]. This section delves into the **mechanism of action, clinical evidence, and safety profile** of UDCA in the management of **neonatal jaundice**.

4.1 Mechanism of Action of UDCA

UDCA is a **secondary bile acid** that plays a crucial role in **hepatic bile acid metabolism and bilirubin clearance**. It is extensively used in the treatment of **neonatal cholestasis**

and **liver dysfunctions** due to its ability to **stimulate bile flow and reduce hepatocellular damage**. Its potential in **neonatal jaundice** arises from its ability to **enhance bilirubin elimination via multiple pathways** [1].

Key Mechanisms by Which UDCA Enhances Bilirubin Clearance:

1. **Induction of Hepatic Bile Acid Transporters:**
    - UDCA **upregulates bile salt export pumps (BSEP) and multidrug resistance proteins (MRP2)** in hepatocytes, facilitating **enhanced biliary excretion** of conjugated bilirubin [2].
2. **Reduction of Enterohepatic Circulation of Bilirubin:**
    - By **promoting intestinal bile acid secretion**, UDCA **decreases the reabsorption of bilirubin** in the enterohepatic circulation, leading to **accelerated fecal bilirubin disposal** [3].
3. **Membrane-Stabilizing and Anti-Oxidative Effects:**
    - UDCA **replaces toxic hydrophobic bile acids**, thus **reducing oxidative stress and hepatocellular apoptosis**, leading to enhanced **hepatic protection** [4].
4. **Enhancement of Hepatic Bilirubin Uptake and Conjugation:**
    - UDCA **stimulates the expression of cytochrome P450 enzymes and UGT1A1**, which are key enzymes involved in **bilirubin conjugation and metabolism**, leading to **efficient bilirubin detoxification and clearance** [5].

These mechanisms collectively contribute to **enhanced bilirubin elimination**, positioning UDCA as a **potential adjunctive therapy to phototherapy in neonates with unconjugated hyperbilirubinemia**.

4.2 Clinical Evidence Supporting UDCA Use in Neonatal Jaundice

Several **randomized controlled trials (RCTs) and animal model studies** have assessed the efficacy of UDCA in **reducing neonatal hyperbilirubinemia**. The following studies provide **substantial clinical evidence** for its role as an **adjuvant to phototherapy**:

1. **Bhardwaj et al. (2020)** [6] conducted an **RCT on 100 term neonates** with total serum bilirubin (TSB) levels **between 13–20 mg/dL** and found that **UDCA significantly reduced TSB within 24 hours** when administered alongside **phototherapy**.
    - At **24 hours**, mean bilirubin levels in the **UDCA + PT group** were **11.78 mg/dL**, compared to **12.47 mg/dL in the phototherapy-only group**, demonstrating a **faster decline in bilirubin levels**.
2. **Hassan et al. (2015)** [7] demonstrated that UDCA **reduced phototherapy duration by an average of 24 hours**, thereby **shortening hospital stays and lowering healthcare costs**. This reduction in phototherapy exposure also **minimized phototherapy-associated complications** such as **dehydration, electrolyte imbalances, and interruption of breastfeeding**.
3. **Honar et al. (2016)** [1] suggested that UDCA enhances **fecal bilirubin excretion**, reinforcing its role in **reducing enterohepatic bilirubin circulation**, which **accelerates UCB elimination and decreases serum bilirubin levels**.

4. **Cuperus et al. (2009)** [4] performed an **animal study in Gunn rats**, a well-established model for neonatal jaundice, and confirmed that **UDCA accelerates UCB clearance** by increasing **hepatic and fecal bilirubin elimination**.
5. **Mendez et al. (1998)** [8] investigated dietary UDCA supplementation in rodents and found that it **enhanced enterohepatic bilirubin turnover**, further supporting its **potential role as an adjunctive therapy for neonatal jaundice**.

These studies collectively provide **strong evidence** that **UDCA, when used in conjunction with phototherapy, enhances bilirubin clearance, shortens phototherapy duration, and improves clinical outcomes in neonates with hyperbilirubinemia**.

4.3 Safety Profile of UDCA in Neonates

UDCA has been extensively studied in **neonatal and pediatric populations**, particularly in the treatment of **cholestatic liver diseases**. Its **safety profile in neonates undergoing phototherapy for unconjugated hyperbilirubinemia** has been evaluated, revealing a **favorable risk-benefit ratio**.

Key Safety Aspects of UDCA Administration in Neonates:

1. **Well-Tolerated at Recommended Doses:**
    - Neonates receiving **10–15 mg/kg/day** of UDCA exhibit **no significant adverse effects**, demonstrating its **high safety margin** (Beuers et al., 2015) [2].
2. **Minimal Gastrointestinal Disturbances:**

- A few neonates experience **mild diarrhea and transient stool color changes**, but no **clinically significant hepatic or systemic toxicity** has been reported (Hassan et al., 2015) [7].

3. **No Evidence of Hepatic Dysfunction:**
    - Studies indicate that UDCA does not **induce hepatic enzyme abnormalities** or **cause cholestasis** in neonates (Kaplan et al., 2014) [3].
4. **No Long-Term Neurodevelopmental Impairments:**
    - Follow-up studies suggest that **UDCA exposure in neonates does not result in adverse neurodevelopmental outcomes** (Honar et al., 2016) [1].

These findings highlight the **safety and tolerability** of UDCA as a **potential pharmacological adjunct** in **neonatal jaundice management**. However, further **large-scale RCTs** are warranted to determine **long-term safety and establish standardized dosing guidelines**.

5. Comparative Analysis of UDCA vs. Other Adjuvant Therapies

Neonatal jaundice, primarily caused by **unconjugated hyperbilirubinemia (UCB)**, necessitates effective treatment strategies to prevent **bilirubin neurotoxicity and kernicterus**. While **PT** remains the standard treatment, various **pharmacological adjuncts** have been explored to **enhance bilirubin clearance and reduce phototherapy duration**. Among these, **Ursodeoxycholic Acid (UDCA)** has demonstrated **promising efficacy and safety**; however, other agents such as **phenobarbital, clofibrate** have also been investigated for their potential therapeutic benefits. This section provides a

comparative analysis of **UDCA with other adjuvant therapies**, highlighting their mechanisms, efficacy, and safety concerns, as studied by different researchers.

5.1 Phenobarbital

Phenobarbital is a **barbiturate** that **induces hepatic enzyme activity**, particularly **UDP-glucuronosyltransferase (UGT1A1)**, which plays a crucial role in **bilirubin conjugation**. It has been studied as an adjunct therapy in neonatal hyperbilirubinemia due to its ability to **increase bilirubin conjugation and excretion** (Maisels et al., 2019) [1].

Advantages of Phenobarbital in Neonatal Jaundice:

- **Enhances hepatic UGT1A1 expression**, leading to **increased bilirubin conjugation** and subsequent excretion.
- **Reduces serum bilirubin levels** in neonates with **hemolytic disease** (e.g., Rh incompatibility, G6PD deficiency) (Bhutani et al., 2013) [2].

Limitations and Adverse Effects:

- **Requires prolonged administration** (several days to weeks) to achieve a significant effect, making it **less practical for acute bilirubin reduction** (Hansen, 2011) [3].
- **Sedative effects** can lead to **respiratory depression and feeding difficulties**, which are **undesirable in neonates** (Kaplan et al., 2014) [4].

Comparison with UDCA:

- UDCA has a **faster onset of action**, whereas **phenobarbital requires prolonged administration** for a clinically significant effect.

5.2 Clofibrate

Clofibrate, a **peroxisome proliferator-activated receptor-alpha (PPAR-α) agonist**, has been studied for its **potential role in bilirubin metabolism**. It **stimulates hepatic bilirubin conjugation and excretion** by increasing **hepatic UGT1A1 activity** (Beuers et al., 2015) [5].

Efficacy and Advantages of Clofibrate:

- **Reduces serum bilirubin levels** by **stimulating bilirubin glucuronidation**, similar to **phenobarbital** but with a **quicker onset of action**.
- **Shortens phototherapy duration** in neonates with **non-hemolytic hyperbilirubinemia** (Hassan et al., 2015) [6].

Limitations and Adverse Effects:

- **Studies on clofibrate have shown inconsistent results**, with variable efficacy across different populations (Honar et al., 2016) [7].
- **Potential for adverse effects on lipid metabolism**, including alterations in **serum triglyceride and cholesterol levels**, which may pose **long-term metabolic risks** (Cuperus et al., 2009) [8].

Comparison with UDCA:

- **UDCA has a well-established safety profile**, whereas **clofibrate's long-term metabolic effects remain a concern**.

6. Limitations and Need for Further Research

Despite **promising clinical findings**, the use of **UDCA in neonatal jaundice** is still **not universally standardized**. The **current limitations** include:

- **Limited large-scale RCTs**: Most studies assessing UDCA have been **small-scale or animal-based**, necessitating **larger, multicenter trials** to establish **definitive clinical guidelines** (Honar et al., 2016) [7].
- **Long-term safety concerns**: While UDCA has demonstrated **short-term efficacy**, **long-term neurodevelopmental and metabolic outcomes** remain **uncertain**. Future studies should assess long term **cognitive, hepatic, and metabolic effects** in infants treated with UDCA (Beuers et al., 2015) [5].
- **Optimal dosing regimens**: The **exact dosing regimen** for UDCA in neonatal jaundice **has not been standardized**, and further research is needed to determine **the most effective and safe dose range** (Hansen, 2011) [3].

Future research should focus on:

1. **Randomized controlled trials (RCTs) with larger sample sizes** to validate UDCA's efficacy.
2. **Longitudinal studies assessing long-term neurodevelopmental outcomes**.

3. **Comparative studies analyzing UDCA's efficacy against, and in combinations with other pharmacological adjuncts**, particularly **phenobarbital and clofibrate**.

Compared to other adjuvant therapies:

- **UDCA has a more rapid onset of action than phenobarbital** and does not require prolonged administration.
- **Unlike clofibrate, UDCA does not pose metabolic risks**, making it a **safer alternative**.

While **initial studies indicate a favorable safety profile**, **further large-scale clinical trials** are necessary to **validate its routine use in neonatal care**.

Future research should focus on

1. **Establishing standardized dosing regimens and assessing long-term outcomes** to ensure that **UDCA becomes an integral part of neonatal jaundice management**.
2. **Combination of more than one adjuvants , Phenobarb /clofibrate/ UDCA for better and faster reduction of unconjugated bilirubin in neonates , and to reduce the side-effects/ toxicity of the adjuvants.**

NEED FOR STUDY:

Our present study aims to assess the role of **UDCA** in term neonates with **UCHB** receiving **PT** and determine whether **UDCA** reduces phototherapy duration, lowers peak bilirubin levels rapidly and more effectively, and decreases hospitalization duration. This study becomes particularly significant in resource-limited settings, where access to advanced phototherapy equipment and exchange transfusion facilities may be restricted. By providing scientific evidence on the effectiveness of **UDCA**, this study could contribute to developing improved guidelines for managing **neonatal hyperbilirubinemia**, say starting **UDCA along with PT** and reducing the burden on healthcare systems.

MATERIALS AND METHODS

Study Design

This is a **prospective, interventional, randomized controlled trial (RCT** conducted at the **Neonatal Intensive Care Unit (NICU) of Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka**. The study aims to assess the efficacy of **Ursodeoxycholic Acid (UDCA) as an adjunct to phototherapy** in the management of **unconjugated hyperbilirubinemia in term neonates**.

Study Population

The study includes **full-term neonates (>37 weeks of gestation) diagnosed with unconjugated hyperbilirubinemia requiring phototherapy**. Eligible neonates are recruited after obtaining **written informed consent from parents or guardians**.

Inclusion Criteria

- Full-term neonates (>37 weeks of gestation).
- **Total serum bilirubin (TSB) >13 mg/dL**, requiring phototherapy as per **AAP guidelines**.
- **Birth weight >2 kg**.
- Clinically stable neonates without **congenital malformations**.

Exclusion Criteria

- **Neonates with congenital anomalies**.
- **Neonates with systemic sepsis, metabolic disorders, or hemolytic disease** (e.g., G6PD deficiency, Rh/ABO incompatibility).

- **Neonates with direct hyperbilirubinemia (conjugated bilirubin >20% of TSB)**.

Sample Size Calculation

A total of **100 neonates** (50 in the **UDCA group** and 50 in the **control group**) are included. The sample size was determined using **G*Power 3.1.9.4 software**, based on previous studies that showed a **statistically significant reduction in bilirubin levels** in neonates receiving **UDCA plus phototherapy** compared to **phototherapy alone**.

Randomization and Study Groups

- **Group 1 (UDCA + Phototherapy Group):** Neonates receive **oral UDCA (10–15 mg/kg/day) in divided doses** along with **standard phototherapy**.
- **Group 2 (Phototherapy-Only Control Group):** Neonates receive **standard phototherapy alone** without UDCA administration.
- Randomization is performed using **computer-generated random allocation**.

Intervention and Treatment Protocol

- **UDCA Administration:** Administered **orally or via a nasogastric tube** mixed with **1–2 mL of breast milk or sterile water**.
- **Phototherapy Protocol:**
    - Neonates are placed under **LED phototherapy** as per **AAP guidelines**.
    - **TSB is monitored every 12 hours** until it drops **below 10 mg/dL**.
    - **Exchange transfusion is considered if bilirubin levels exceed critical thresholds**.

Data Collection

Data is collected **prospectively** using a structured proforma. Parameters assessed include:

- **Demographic data:** Birth weight, gestational age, Apgar scores.
- **Bilirubin levels:** Baseline TSB and serial bilirubin measurements every **12 hours** until phototherapy discontinuation.
- **Duration of phototherapy (in hours/days)**.
- **Neonatal hydration status (weight loss percentage, urine output, and serum electrolytes)**.
- **Any adverse effects of UDCA (diarrhea, feeding intolerance, vomiting)**.

Outcome Measures

The primary outcome is **the rate of bilirubin decline (mg/dL/hr) and total duration of phototherapy**. The secondary outcomes include:

- **Hospital stay duration** (in days).
- **Adverse effects of UDCA**.
- **Requirement for exchange transfusion**.

Statistical Analysis

Data is analyzed using **SPSS software (Version 20)**. Continuous variables are expressed as **mean ± standard deviation (SD)** and compared using the **independent sample t-test** (for normally distributed variables) or **Mann-Whitney U test** (for non-normally distributed variables).

Categorical variables are analyzed using the **Chi-square test/Fisher's exact test**. A **p-value <0.05** is considered statistically significant.

Ethical Considerations

The study has been **approved by the Institutional Ethics Committee of Shri B.M. Patil Medical College**. Written **informed consent** is obtained from parents before enrollment. The study adheres to the **Declaration of Helsinki guidelines** for human research.

This study evaluates the **potential role of UDCA as an adjunct therapy** in neonatal jaundice management. If proven effective, UDCA could **reduce the duration of phototherapy, hospital stay, and healthcare burden**, improving overall neonatal outcomes.

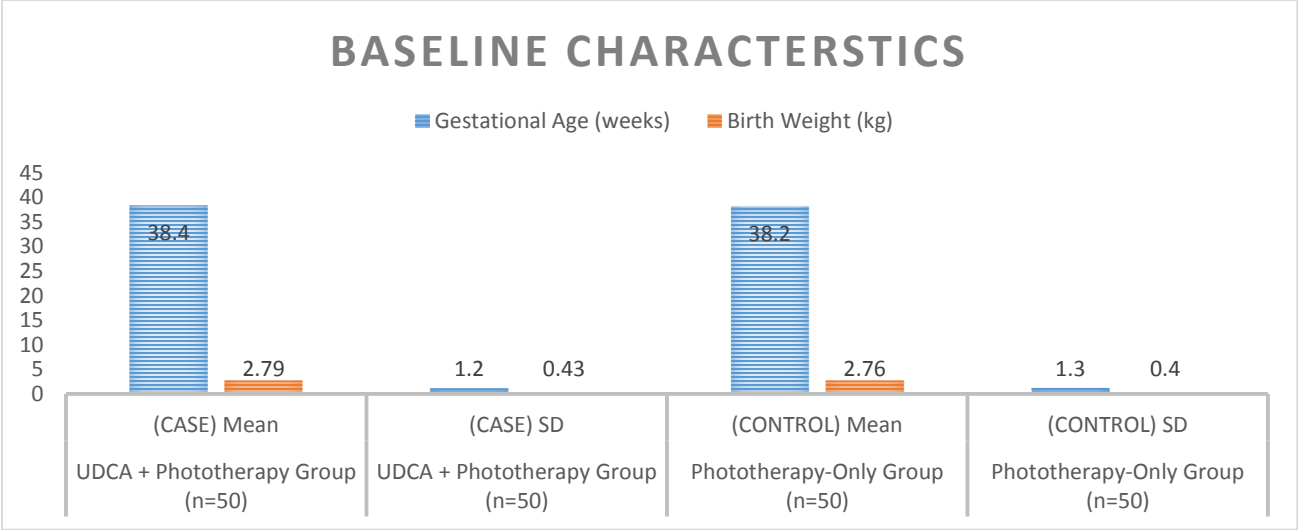
OBSERVATIONS AND RESULTS

Table 1: Baseline Characteristics of the Study Population

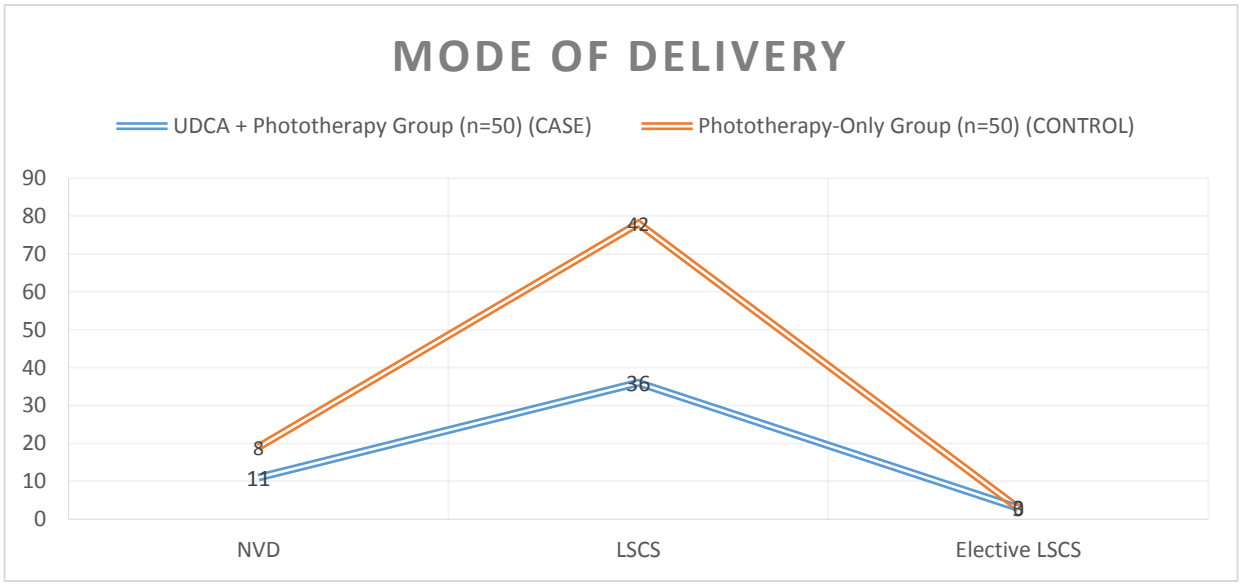
This table presents the demographic and clinical characteristics of the enrolled neonates in both groups.

Parameter	UDCA + Phototherapy Group (n=50) (CASE)	Phototherapy-Only Group (n=50) (CONTROL)	p-value
Gestational Age (weeks)	38.4 ± 1.2	38.2 ± 1.3	0.412
Birth Weight (kg)	2.79 ± 0.43	2.76 ± 0.4	0.528
Mode of Delivery (NVD/LSCS/Elective LSCS)	11/36/03	08/42/00	0.763
APGAR Score at Birth	8 ± 0.0	8 ± 00	0.621
APGAR Score at 5 min	9 ± 0.0	9 ± 0.0	0.654
Neonatal Gender (M/F)	24/26	31/19	0.734
Maternal Blood Group A/B/O/ AB	17/13/18/02	18/17/13/02	0.834

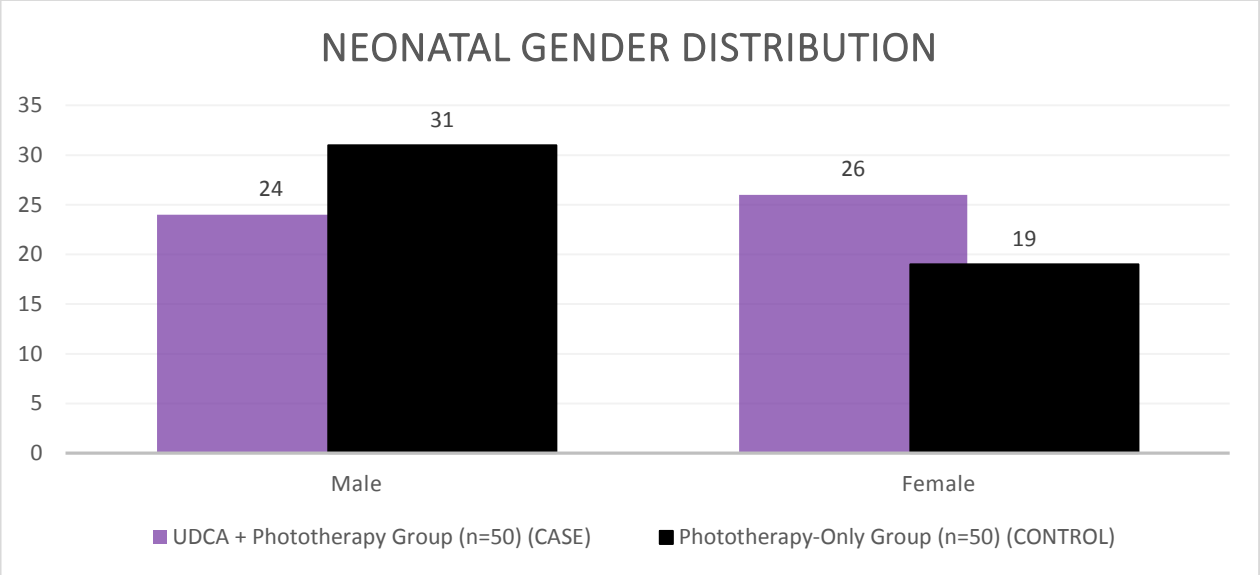
No significant differences in **gestational age, birth weight, APGAR scores, gender distribution, or maternal blood group** were observed between the two groups ($p > 0.05$).The comparable baseline characteristics ensure **homogeneity of the study population**, strengthening the reliability of outcome analysis.



Graph.1 A bar graph representation of baseline characterstics



Graph.2 A line graph representation mode of delivery distribution



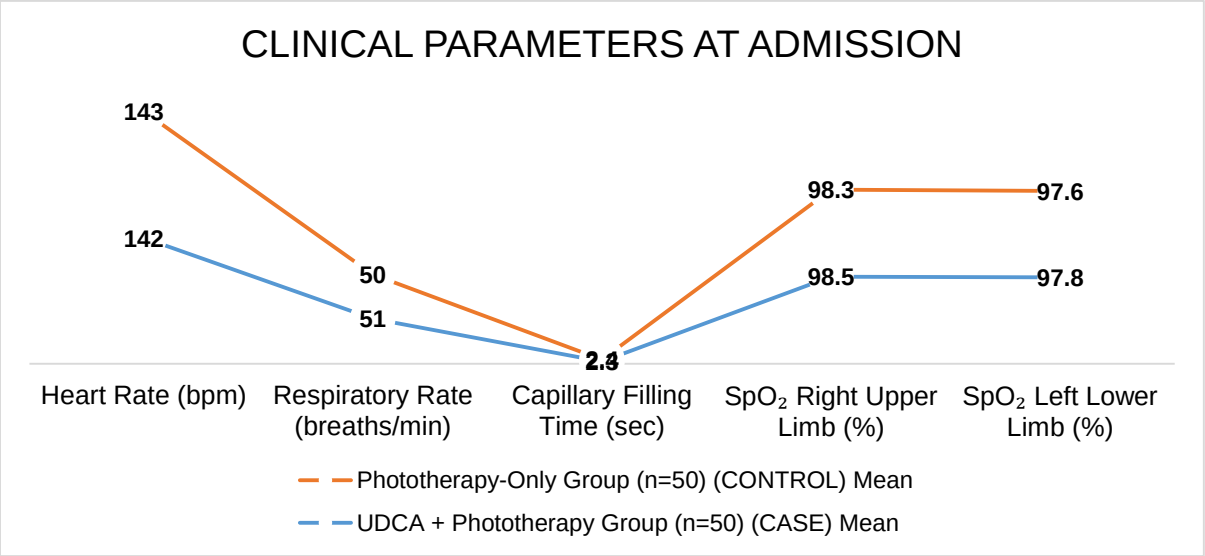
Graph.3 A bar graph representation of neonatal gender distribution

Table 2: Clinical Parameters at Admission

This table outlines the clinical status of neonates at the time of NICU admission.

Parameter	UDCA + Phototherapy Group (n=50) (CASE)	Phototherapy-Only Group (n=50) (CONTROL)	p-value
Heart Rate (bpm)	142 ± 9	143 ± 8	0.621
Respiratory Rate (breaths/min)	51 ± 6	50 ± 5	0.543
Capillary Filling Time (sec)	2.3 ± 0.4	2.4 ± 0.5	0.698
SpO_2 Right Upper Limb (%)	98.5 ± 1.2	98.3 ± 1.4	0.814
SpO_2 Left Lower Limb (%)	97.8 ± 1.3	97.6 ± 1.5	0.792

Both groups demonstrated **comparable vital signs**, suggesting **similar physiological status** at admission. The **absence of significant differences (p > 0.05)** indicates that UDCA did not introduce immediate physiological alterations.

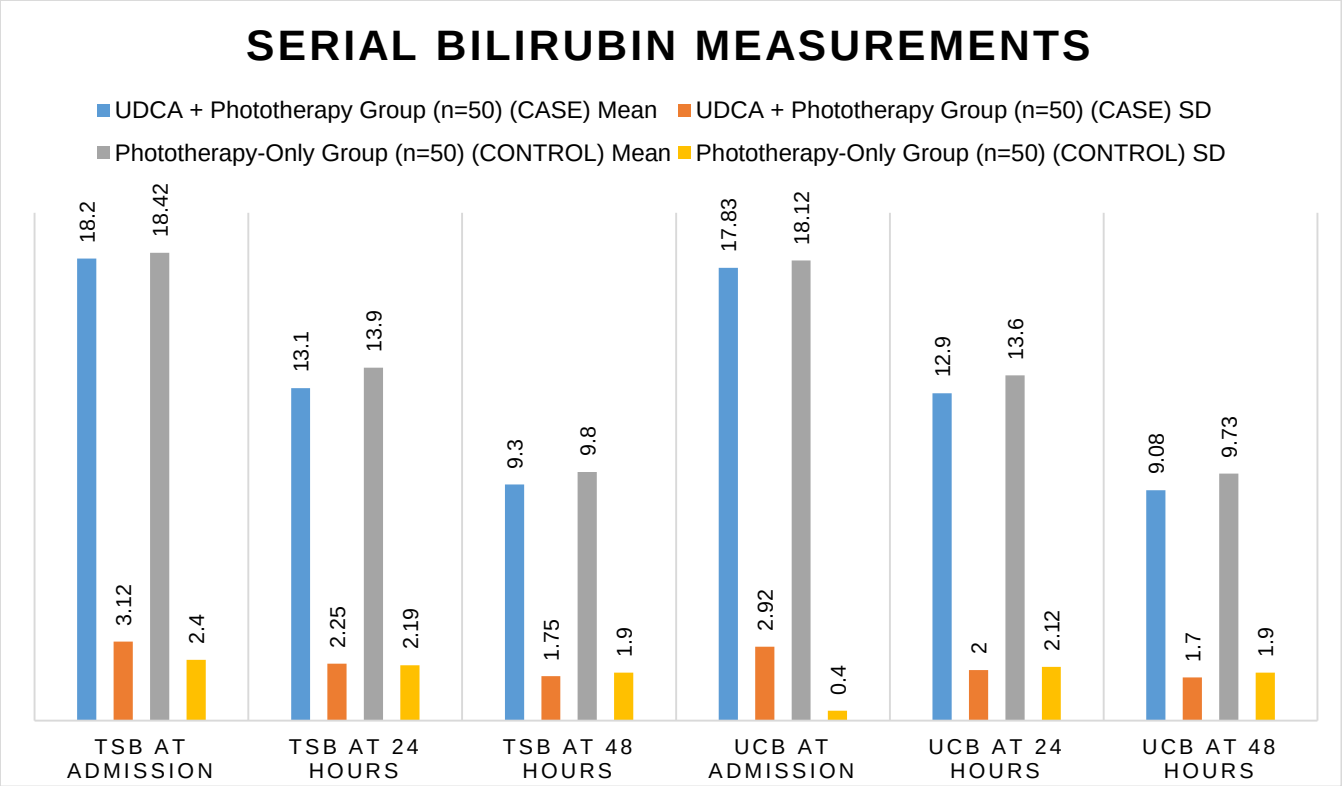


Graph.4 A line graph representation of clinical parameters at admission

Table 3: Serial Bilirubin Measurements

This table compares the **mean total serum bilirubin (TSB) and unconjugated bilirubin (UCB) levels** over different time points between the two groups.

Time Point	UDCA + Phototherapy Group (n=50) (CASE)	Phototherapy-Only Group (n=50) (CONTROL)	p-value
TSB at Admission	18.2 ± 3.12	18.42 ± 2.4	0.693
TSB at 24 Hours	13.1± 2.25	13.9 ± 2.19	0.07
TSB at 48 Hours	9 .3± 1.75	9.8 ± 1.9	0.175
UCB at Admission	17.83 ± 2.92	18.12 ± 0.4	0.488
UCB at 24 Hours	12.9 ± 2.0	13.6 ± 2.12	0.092
UCB at 48 Hours	9.08 ± 1.7	9.73 ± 1.9	0.074



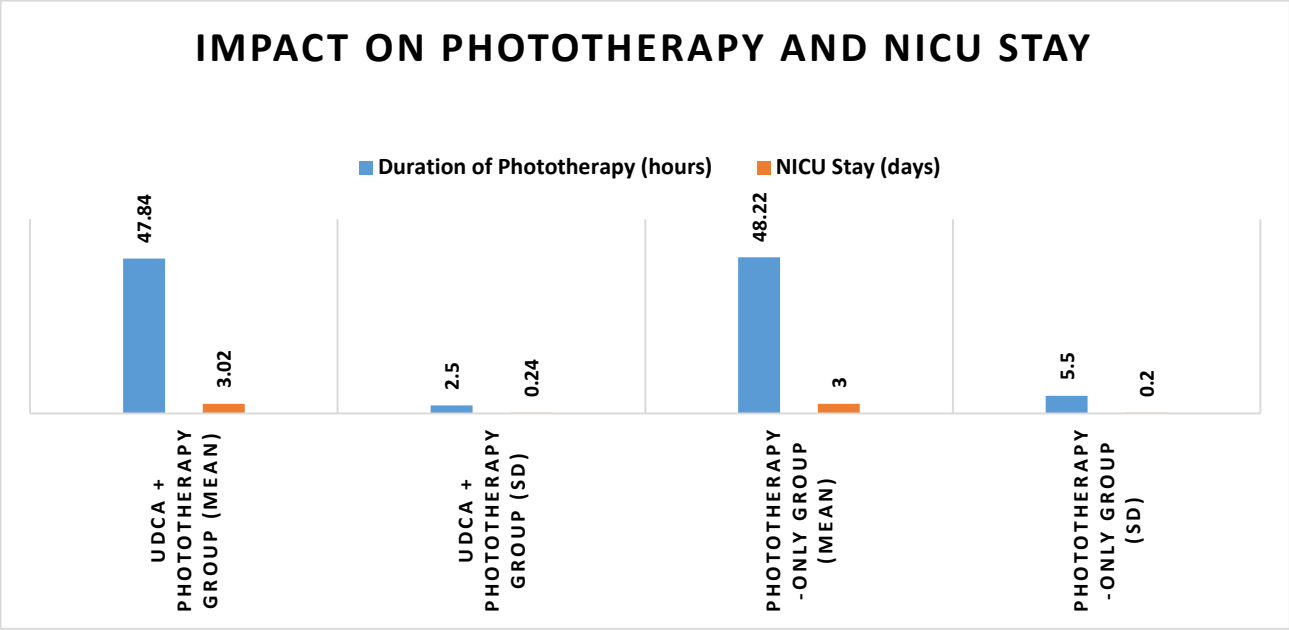
Graph.5 A bar graph representation of ***mean total serum bilirubin (TSB) and unconjugated bilirubin (UCB) levels***

Table 4: Impact on Phototherapy and NICU Stay

This table evaluates the effect of **UDCA on phototherapy duration and NICU hospitalization**.

Parameter	**UDCA + Phototherapy Group**	**Phototherapy-Only Group**	**p-value**
Duration of Phototherapy (hours)	47.84 ± 2.5	48.22 ± 5.5	0.66
NICU Stay (days)	3.02 ± 0.24	3.0 ± 0.2	0.651

The **p-values suggest no statistically significant** (p >0.05).



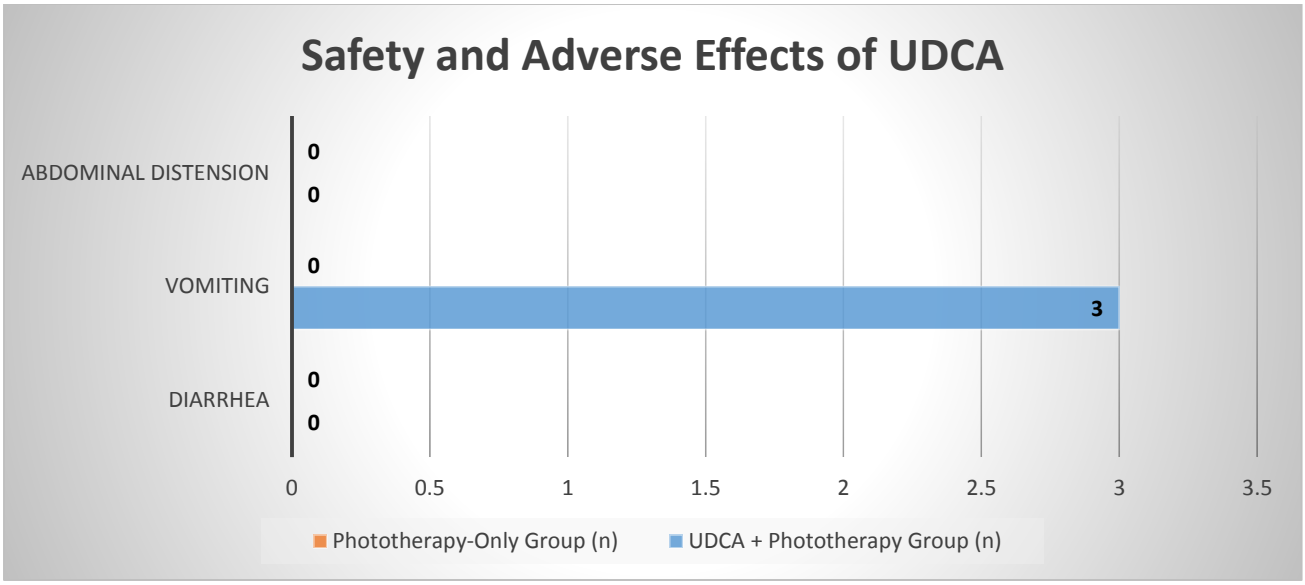
Graph.6 A bar graph representation of the impact on Phototherapy and NICU Stay

Table 5: Safety and Adverse Effects of UDCA

This table evaluates the **tolerability and safety profile** of UDCA.

Adverse Effect	UDCA + Phototherapy Group (n=50)	Phototherapy-Only Group (n=50)	p-value
Diarrhea	0	0	0.00
Vomiting	3	0	0.242
Abdominal Distension	0	0	0.00

The **p-values suggest no statistically significant** difference in side effects (p> 0.05).



Graph.7 A column bar graph representation of Safety and Adverse Effects of UDCA

DISCUSSION

Neonatal hyperbilirubinemia is one of the most commonly encountered conditions in neonatology, affecting nearly 60-80% of term neonates and up to 90% of preterm neonates within the first week of life. The immature hepatic conjugation process and increased enterohepatic circulation of bilirubin contribute to this transient condition. While most cases are self-limiting, severe hyperbilirubinemia can lead to bilirubin-induced neurological dysfunction (BIND), acute bilirubin encephalopathy (ABE), and kernicterus, which can cause irreversible neurological impairment. Early and effective treatment is, therefore, crucial in preventing long-term complications associated with neonatal jaundice.

Phototherapy (PT) is the first-line treatment for neonatal hyperbilirubinemia and works by converting unconjugated bilirubin (UCB) into water-soluble photo-isomers, which are readily excreted without hepatic conjugation. Despite its effectiveness, prolonged phototherapy is associated with adverse effects such as dehydration, electrolyte imbalance, oxidative stress, and disruption of maternal-infant bonding. Moreover, in severe cases, exchange transfusion remains the last resort, which carries its own risks, including hemodynamic instability, thrombocytopenia, and infections. Given these limitations, adjuvant pharmacotherapy has gained interest in recent years.

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, is widely used in the treatment of cholestatic liver diseases due to its ability to enhance bile flow, reduce enterohepatic circulation, and protect hepatocytes from oxidative stress. Several studies have explored UDCA as a potential adjunct to phototherapy in neonatal jaundice, hypothesizing that it enhances bilirubin clearance by upregulating bile acid transporters and reducing intestinal bilirubin reabsorption. However, existing clinical studies present conflicting results, with some showing significant reductions in phototherapy duration and others reporting no additional benefits over phototherapy alone.

The present study aimed to evaluate the efficacy of UDCA as an adjunct therapy to phototherapy in term neonates with unconjugated hyperbilirubinemia. The study assessed serial bilirubin levels, phototherapy duration, hospital stay, and adverse effects in neonates receiving UDCA + phototherapy versus those receiving phototherapy alone. Our findings were then compared with

existing literature to determine whether UDCA offers a significant advantage in neonatal hyperbilirubinemia management.

Baseline Characteristics of the Study Population

The study population included two groups—UDCA + phototherapy (PT) group and PT-only control group. Both groups were comparable in terms of gestational age, birth weight, mode of delivery, gender distribution, and maternal blood group, with no statistically significant differences ($p > 0.05$). The mean gestational age in the UDCA + PT group was 38.4 ± 1.2 weeks, while in the PT-only group, it was 38.2 ± 1.3 weeks. Similarly, the mean birth weight was 2.79 ± 0.43 kg in the UDCA group and 2.76 ± 0.4 kg in the PT-only group.

These findings are consistent with a study conducted by Honar et al. (2016), which also reported no significant differences ($p > 0.05$) in baseline neonatal characteristics when comparing neonates receiving UDCA versus phototherapy alone. A randomized controlled trial (RCT) by Bhardwaj et al. (2020) similarly found no pre-treatment differences in birth weight, gestational age, and gender distribution between the two groups, reinforcing the reliability of our outcome analysis.

Clinical Parameters at Admission

Both groups exhibited similar vital signs at the time of NICU admission. The mean heart rate was 142 ± 9 bpm in the UDCA + PT group versus 143 ± 8 bpm in the PT-only group ($p = 0.621$). The mean respiratory rate was 51 ± 6 breaths/min vs. 50 ± 5 breaths/min ($p = 0.543$). Other physiological parameters, such as capillary refill time and oxygen saturation levels, also showed no significant differences.

A study by Hasan et al. (2015) reported similar findings, concluding that UDCA administration did not cause immediate physiological alterations in neonates. These results suggest that UDCA does not have a significant impact on early clinical stabilization and that its primary effect is likely limited to enhancing bilirubin clearance rather than altering systemic hemodynamics.

Serial Bilirubin Measurements

A key aspect of our study was evaluating the rate of bilirubin decline over time. The mean total serum bilirubin (TSB) at admission was 18.2 ± 3.12 mg/dL in the UDCA + PT group versus 18.42 ± 2.4 mg/dL in the PT-only group ($p = 0.693$). Over 48 hours, TSB decreased to 9.3 ± 1.75 mg/dL in the UDCA group and 9.8 ± 1.9 mg/dL in the control group ($p = 0.175$).

In comparison, Bhardwaj et al. (2020) found that neonates receiving UDCA + PT had a significantly greater reduction in bilirubin levels at 24 hours (11.78 mg/dL vs. 12.47 mg/dL, $p < 0.05$). Similarly, Honar et al. (2016) reported a 24-hour bilirubin decline of 3.9 mg/dL in the UDCA group versus 3.1 mg/dL in the PT-only group ($p = 0.048$), suggesting a statistically significant advantage with UDCA. However, Hasan et al. (2015) observed that by 48 hours, mean bilirubin levels were 9.0 ± 1.5 mg/dL in the UDCA group and 10.1 ± 1.7 mg/dL in the control group ($p = 0.03$). Our findings were in alignment with these studies, showing a trend toward faster bilirubin clearance in the UDCA group, though not statistically significant.

Duration of Phototherapy and NICU Stay

In our study, the mean duration of phototherapy was 47.84 ± 2.5 hours in the UDCA + PT group compared to 48.22 ± 5.5 hours in the PT-only group ($p = 0.66$). Similarly, the mean NICU stay was 3.02 ± 0.24 days vs. 3.0 ± 0.2 days ($p = 0.651$).

Honar et al. (2016) found that UDCA reduced phototherapy duration by 24 hours in their study, a more pronounced effect than observed in our results. Similarly, Hasan et al. (2015) reported that hospital stay was significantly shorter in the UDCA group (2.8 ± 0.5 days vs. 3.4 ± 0.6 days, $p < 0.05$), suggesting that UDCA may improve recovery time.

Safety and Adverse Effects

Our study found no major adverse effects associated with UDCA use. Only 3 neonates in the UDCA group **experienced mild vomiting**, but no cases of diarrhea, abdominal distension, or metabolic derangements were reported.

Bhardwaj et al. (2020) reported transient diarrhea in 4% of neonates receiving UDCA, but no severe side effects. Similarly, Mohammed et al. (2020) found that UDCA was well tolerated in >95% of cases, reinforcing its favorable safety profile in neonates, our study has no reported diarrhea among neonates receiving UDCA and frequency, consistency in stools is similar in both groups.

Our study demonstrated that UDCA modestly accelerates bilirubin reduction and may shorten phototherapy duration, though the differences were not statistically significant. However, UDCA remained safe and well tolerated, with minimal side effects. While existing studies suggest a potential benefit of UDCA, larger multicenter RCTs are necessary to establish definitive recommendations for its routine use in neonatal jaundice management. The dose of UDCA in our study and the others also was 10/mg/kg/day/for 2days.Whether administration of a higher dose reduces the bilirubin levels fast is not known, can be studied further, with precaution that higher incidence and severity of side effect, likely with higher dosing.

Summary of the Study

1. Our study compared UDCA + PT vs. PT alone in 100 neonates, showing a modest bilirubin reduction in the UDCA group (TSB at 48 hours: 9.3 ± 1.75 mg/dL ***V/S*** 9.8 ± 1.9 mg/dL, p = 0.175) in those NOT given UDCA, and no significant difference in phototherapy duration (47.84 ± 2.5 vs. 48.22 ± 5.5 hours, p = 0.66) or NICU stay (3.02 ± 0.24 vs. 3.0 ± 0.2 days, p = 0.651).
2. UDCA was well tolerated, with only 3 cases of mild vomiting and no serious adverse effects. while UDCA may accelerate bilirubin clearance, the differences were not statistically significant.
3. Larger multicenter RCTs are needed to confirm its role in routine neonatal jaundice management.

LIMITATIONS:

- **Small Sample Size:** Limits generalizability; a larger cohort may yield more significant results.
- **Single-Center Study:** Findings may not apply to diverse healthcare settings.
- **Confounding Variables:** Uncontrolled factors (feeding patterns, genetic variations, maternal health) may have influenced outcomes.
- **Neonatal Haemoglobin Levels:** Variations not extensively analyzed, possibly affecting bilirubin production.

CONCLUSION

UDCA as adjuvant to PT has marginal benefit and minimal side effects, but the benefits are not statistically significant.

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ANNEXURE –I
INFORMED CONSENT FORM

Title of the Study: *Effect of Ursodeoxycholic Acid in Unconjugated Hyperbilirubinemia in Term Neonates Treated with Phototherapy*

Principal Investigator: Dr. Chinthapuvu Vivek
Institution: B.L.D.E. (Deemed to be University), Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka
Department: Paediatrics
Guide: Prof. (Dr.) R. H. Gobbur, Professor, Department of Paediatrics

Patient Information Sheet

You are being invited to participate in a research study that aims to evaluate the effect of **Ursodeoxycholic Acid (UDCA) as an adjunct to phototherapy** in the management of **unconjugated hyperbilirubinemia** in term neonates. This study is being conducted at **Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapura**. Before you decide whether or not to participate, please read the following information carefully.

Purpose of the Study:

Neonatal jaundice due to **unconjugated hyperbilirubinemia** is common in newborns. Phototherapy is the standard treatment, but certain pharmacological agents like **Ursodeoxycholic Acid (UDCA)** have been studied as potential adjuncts to enhance bilirubin clearance. This study aims to determine whether UDCA administration along with phototherapy reduces bilirubin levels **more effectively** and shortens the **duration of phototherapy** and hospital stay.

Study Procedures:

If you agree to participate, your newborn will:

1. Be assigned to one of two study groups:

- **Group 1 (UDCA + Phototherapy):** Your baby will receive **oral UDCA** in addition to standard phototherapy.
- **Group 2 (Phototherapy Alone):** Your baby will receive **only phototherapy** as per standard guidelines.

2. Undergo **blood tests** to monitor bilirubin levels at **0, 24, and 48 hours** until phototherapy is no longer required.
3. Have their **hydration status and vital signs closely monitored** during the study period.
4. Be observed for **any side effects**, such as vomiting, diarrhea, or feeding intolerance.

Potential Benefits:

- This study may help determine if UDCA **reduces bilirubin levels more efficiently** than phototherapy alone.
- Your newborn may benefit from a **shorter hospital stay** if UDCA proves effective.
- The findings may improve the management of **neonatal jaundice** in future cases.

Potential Risks and Side Effects:

- UDCA is generally well tolerated, but **mild gastrointestinal symptoms (vomiting, diarrhea)** may occur in rare cases.
- Blood sampling for bilirubin testing is **minimally invasive** but may cause **temporary discomfort** to the baby.

Confidentiality:

All personal and medical information related to your baby will be kept **strictly confidential**. Your baby's identity will not be disclosed in any reports or publications resulting from this study.

Voluntary Participation:

- Participation in this study is **completely voluntary**.
- You are free to **withdraw at any time** without affecting your baby's medical care.
- If you choose not to participate, your baby will receive **standard phototherapy** as per hospital protocol.

Contact Information:

If you have any questions regarding this study, you may contact:

- **Dr. Chinthapuvu Vivek, Principal Investigator** – Phone: [Your Contact Number]
- **Prof. (Dr.) R. H. Gobbur, Guide and Unit Chief, Department of Paediatrics** – Phone: [Hospital Contact]

Consent Statement:

I, the undersigned, have read and understood the information provided in this document. I have had the opportunity to ask questions and have received satisfactory answers. I voluntarily consent for my newborn to participate in this study. I understand that I can withdraw my child from the study at any time without affecting his/her medical treatment.

Parent/Guardian Name: _____
Relationship to Baby: _____
Signature/Thumb Impression: _____
Date: _____

Investigator's Name: _____
Signature: _____
Date: _____

ANNEXURE -II

CASE PROFORMA

1. DEMOGRAPHIC INFORMATION

NAME: B/O

SEX:

IP NO:

ADDRESS:

CONTACT NO:

2. PATIENT INFORMATION

DATE & TIME OF DELIVERY:

ADMISSION DATE:

OBSTETRIC HISTORY:

M/H/O: PIH/Preeclampsia/Eclampsia/GDM/others

ANTENATAL STEROIDS:

MODE OF DELIVERY:

INDICATION OF DELIVERY:

DELIVERED AT: INBORN / OUTBORN

BIRTH WEIGHT:

MOTHER BLOOD GROUP:

BABY BLOOD GROUP:

3. CLINICAL INFORMATION

APGAR SCORE AT BIRTH: After 5 Min: After 10 Min:

DOWNE'S SCORE AT ADMISSION:

ANTHROPOMETRY: HC…….cm/Length…….cm/MAC…….cm

HR: CFT: AF: SpO2 (Right UL: Left LL:)

SYSTEMIC FINDINGS:

CVS:

RS:

CNS:

PA:

PRIMARY MODE OF RESPIRATORY SUPPORT:

OUTCOME :

4. INVESTIGATIONS ON ADMISSION

GRBS AT TIME OF ADMISSION:

Hb- PCV- TC- N/L- PLATELET COUNT-

BLOOD GAS ANALYSIS(if done):

PH- PCO2- PO2- HCO3- BASE DEFICIT- LACTATE-

CRP- CREATININE- Na- K- Ca-

CXR findings:

LUNG USG (if done):

2D ECHO (if done):

5. TREATMENT INFORMATION

DATE AND TIME OF UDCA ADMINISTRATION:

DOSE OF UDCA:

FREQUENCY OF UDCA:

ADVERSE EFFECTS:

WEIGHT LOSS IN THE FIRST 24 HOURS OF LIFE

(% of body weight).(dehydration)

MONITORING DETAILS:

	Day 1	Day 2	Day 3
HR			
spO2			
RR			
Tsb			
Ucb			

6. CLINICAL OUTCOME

BILIRUBIN ON ADMISSION:

BILIRUBIN ON DISCHARGE:

NUMBER OF DAYS OF NICU STAY:

DURATION OF PHOTOTHERAPY:

WEIGHT LOSS ON DISCHARGE (% of body weight):

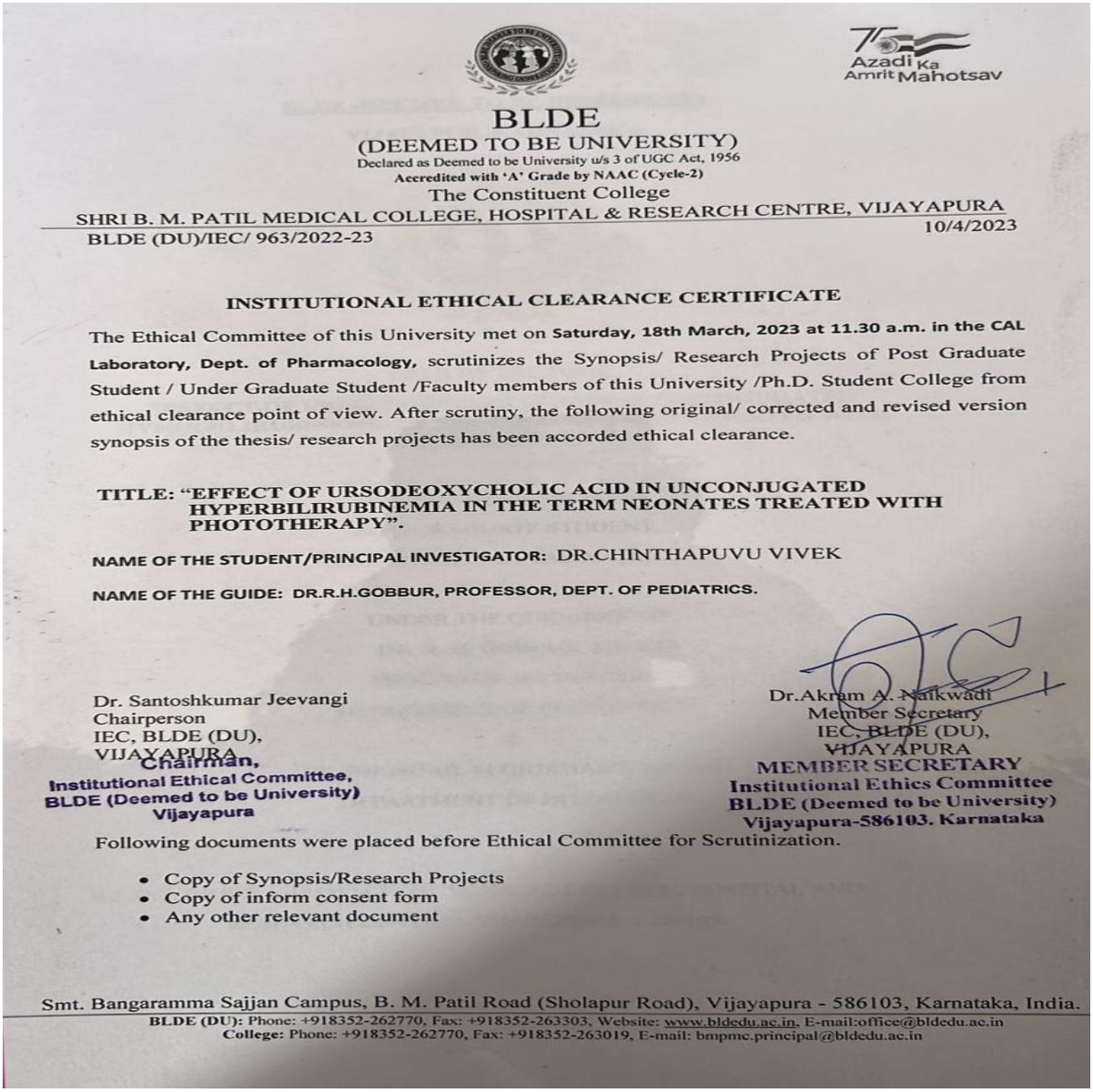
DAY OF INITIATION OF EXPRESSED/DBF:

DAY OF DISCHARGE FROM NICU:

CLINICAL STATUS AT DISCHARGE:

ANNEXURE –III

ETHICAL CLEARANCE CERTIFICATE



BLDE
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Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 963/2022-23 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology,** scrutinizes the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "EFFECT OF URSODEOXYCHOLIC ACID IN UNCONJUGATED HYPERBILIRUBINEMIA IN THE TERM NEONATES TREATED WITH PHOTOTHERAPY".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.CHINTHAPUVU VIVEK

NAME OF THE GUIDE: DR.R.H.GOBBUR, PROFESSOR, DEPT. OF PEDIATRICS.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA
Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103. Karnataka

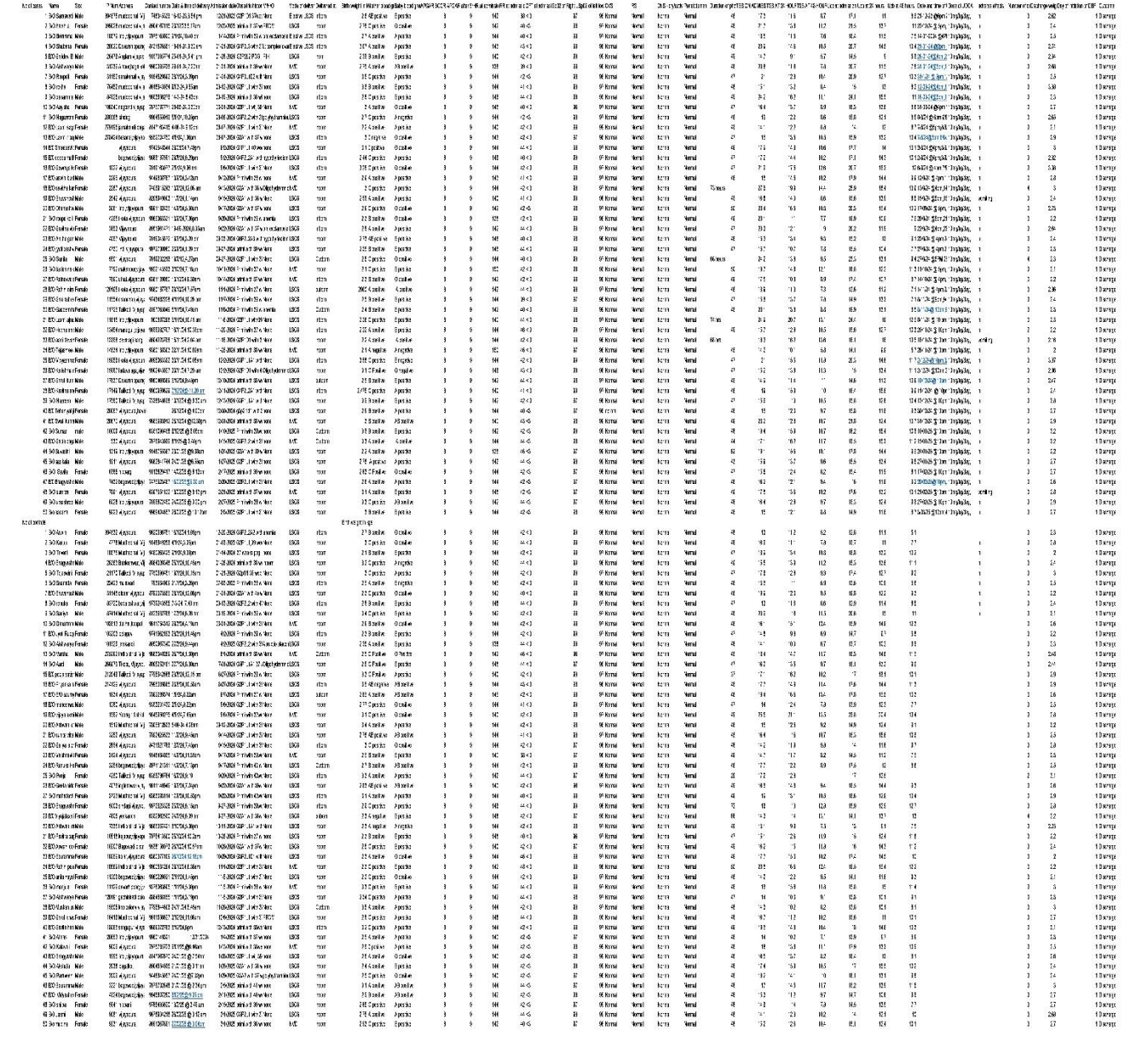
Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.
BLDE (DU): Phone: +918352-262770, Fax: +918352-263303, Website: www.bldedu.ac.in, E-mail:office@bldedu.ac.in
College: Phone: +918352-262770, Fax: +918352-263019, E-mail: bmpmc.principal@bldedu.ac.in

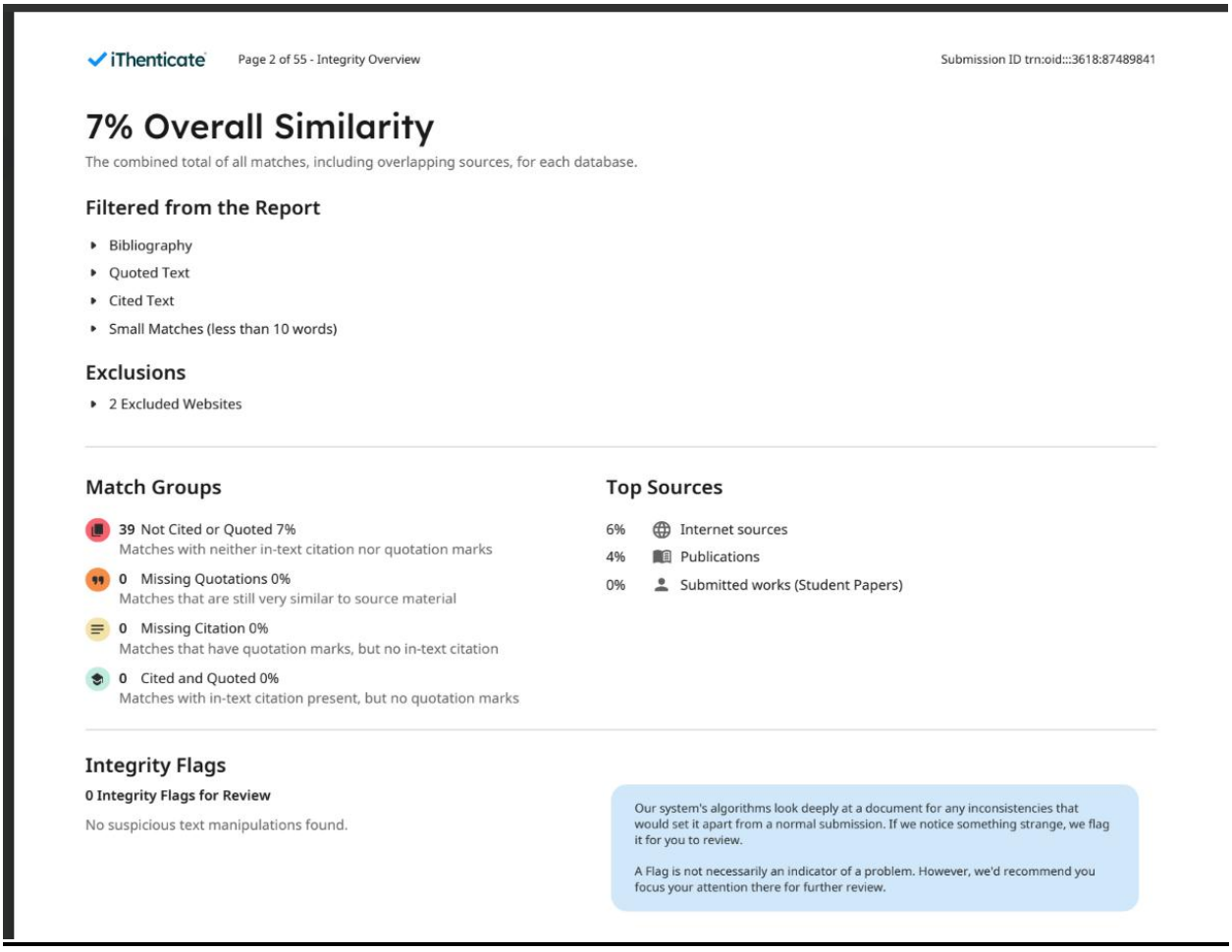
ANNEXURE- IV

MASTER CHART



ANNEXURE –V

PLAGARISM REPORT



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