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COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF MEDICAL LABORATORY SCIENCES

Effect of Phototherapy on Hematological Profile of Newborns with Unconjugated Hyperbilirubinemia at Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia.

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This is to certify that the thesis prepared by Kidist Ababu, entitled: Effect of phototherapy on hematological profile of newborns with unconjugated hyperbilirubinemia at Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia and submitted in partial fulfillment of the requirements for Master of Science degree in Clinical Laboratory Sciences (Hematology and Immunohematology) complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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List of abbreviations

AAP	American Academy of Pediatrics
DNA	Deoxyribonucleic Acid
HCT	Hematocrit
Hgb	Hemoglobin
IHB	Indirect Hyperbilirubinemia
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MPV	Mean Platelet Volume
PT	Phototherapy
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SPHMMC	Saint Paul's Hospital Millennium Medical College
SPSS	Statistical Package for the Social Sciences
TNF	Tumor Necrosis Factor
TSB	Total Serum Bilirubin
WBC	White Blood Cell

Abstract

Background: Newborns frequently experience unconjugated hyperbilirubinemia, which can lead to severe complications if left untreated. Phototherapy, a non-invasive and effective treatment, converts bilirubin into water-soluble forms. Despite its overall safety, phototherapy is discovered to be linked with various adverse effects and its effects on hematological profiles need more investigation.

Objective: To assess the effect of phototherapy on hematological profile of newborns with unconjugated hyperbilirubinemia at Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia from February to April 2024.

Methods: A cross-sectional study was conducted at Saint Paul's Hospital Millennium Medical College from February to April 2024, involving 195 newborns exhibiting unconjugated hyperbilirubinemia to determine effects of phototherapy in their hematological profiles. The participants were selected using a convenient sampling technique. The study employed the Mindray BC-6800plus auto hematology analyzer. The analysis was performed using a paired t-test in SPSS version 25, with a p-value of less than 0.05 considered statistically significant.

Result: Out of a total 195 newborn participants 152 (77.9%) were male. Statistically significant changes in several hematological parameters determined. RBC counts decreased from 4.74 to 4.43 x 10^12 / L ($p < 0.001$), hemoglobin levels from 168.1 to 162.0 g/L ($p < 0.001$), and hematocrit from 45.17% to 44.19% ($p = 0.003$), with significant reductions at 24 and 48 hours ($p < 0.01$) but not at 72 hours. WBC counts increased from 9.90 to 11.02 x 10^9 / L ($p < 0.001$), along with a rise in lymphocyte percentage ($p < 0.001$) and a decrease in monocyte percentage decreased from 8.68% to 7.12% ($p < 0.001$) at 24 and 48 hours but not at 72 hours. Additionally, MCHC decreased from 372.2 g/L to 365.6 g/L ($p = 0.022$), and RDW decreased from 16.16% to 15.83% ($p = 0.005$), platelet count decrease from 220.52 to 207.72 10^9 / L ($p < 0.001$). Other parameters did not exhibit significant changes.

Conclusion: Phototherapy was found to significantly decrease bilirubin levels, RBC count, hemoglobin levels, HCT, MCHC, monocyte percentage, and platelet count while WBC count increased, along with lymphocyte percentage. To optimize newborn care, it is essential to monitor hematological parameters closely during phototherapy.

Key words: *Phototherapy, Hematological Profile, Unconjugated hyperbilirubinemia, Newborn*

1. Introduction

1.1. Background

Newborns commonly experience transient indirect hyperbilirubinemia (IHB), evident as jaundice yellowing of the skin, sclera, and mucous membranes. Biochemically, IHB involves elevated indirect serum bilirubin (ISB), leading to increased total serum bilirubin (TSB). Although most cases are benign, a small percentage requires treatment for severe IHB (1). Jaundice affects 50% of term and 80% of preterm infants in the first week (2). Jaundice develops two to four days it can lead to hospital readmission after early discharge but usually resolves within two weeks without treatment (3).

Most newborns with hyperbilirubinemia experience physiological jaundice, which typically arises within the first few days of life and is generally benign without underlying illness. This condition stems from increased bilirubin production, linked to a shortened lifespan of red blood cells and elevated red cell mass. Decreased bilirubin excretion is also a factor, attributed to low concentrations of hepatocyte binding proteins, reduced glucuronosyl transferase activity, and heightened enterohepatic circulation common in newborns (4).

Breastfed infants are particularly prone to hyperbilirubinemia during the first week of life, thought to be exacerbated by decreased caloric intake and increased enterohepatic circulation of bilirubin. In some cases, breast milk jaundice syndrome may prolong unconjugated hyperbilirubinemia beyond the second week, although its precise mechanism remains unclear. Non-physiological causes of neonatal hyperbilirubinemia include hemolysis from various sources, infections, bruising, blood group incompatibilities (such as rhesus or ABO issues), and metabolic disorders. Rarely, conditions like Gilbert's syndrome and Crigler-Najjar syndrome may also contribute to neonatal hyperbilirubinemia (5).

Unconjugated bilirubin can pose a risk by crossing the blood-brain barrier in newborns. Symptoms of acute bilirubin encephalopathy include lethargy, hypotonia, hypertonia, agitation, apnea, and seizures. Chronic bilirubin encephalopathy, known as kernicterus, may lead to athetoid cerebral palsy, hearing loss, failure to gaze upward and dental enamel dysplasia. In preterm newborns, the more permeable blood-brain barrier and reduced albumin binding affinity

increase the potential for bilirubin toxicity and long-term neurological consequences at lower TSB levels compared to term infants (6).

Severe Infantile Hyperbilirubinemia is often inversely related to gestational age, primarily due to underdeveloped erythropoietin, hepatic, and gastrointestinal systems in premature infants (7, 8). Early detection and prompt intervention are crucial to prevent severe damage to the nervous system from elevated serum bilirubin levels. Primary treatments for neonatal hyperbilirubinemia in clinical settings include liver enzyme inducers, albumin, intravenous immunoglobulin (9), phototherapy and blood exchange therapy (10).

Phototherapy, a non-invasive and highly effective treatment for neonatal hyperbilirubinemia, uses visible light to convert conjugated bilirubin into water-soluble substances. It serves as a primary alternative to exchange transfusion, recommended by the American Academy of Pediatrics (AAP). AAP guidelines consider factors like newborn age, total serum bilirubin levels, gestational age, and individual risk factors to inform healthcare professionals about the optimal timing for phototherapy initiation, preventing neurotoxic consequences of elevated unconjugated bilirubin (7, 11).

Its effectiveness depends on factors like light wavelength, intensity, distance, and body surface area exposed. Commonly using white and blue-green spectrum light, especially the AAP-recommended 460-490 nm range, phototherapy's safety is enhanced by filtering harmful UV rays. Blue light, noted for efficient bilirubin absorption and antibacterial properties, is particularly favored in this treatment (7).

Phototherapy is a widely accepted treatment for neonatal hyperbilirubinemia, primarily targeting unconjugated bilirubin to prevent its accumulation and associated neurological complications. The mechanism involves the exposure of newborns' skin to specific wavelengths of light, typically in the blue-green spectrum (460-490 nm), which is absorbed by bilirubin molecules in the skin. This absorption leads to photoisomerization of bilirubin, converting it into water-soluble forms that are readily excreted through urine and stool, bypassing the liver's need for conjugation (12).

The burden of severe neonatal jaundice (SNJ) is a significant concern globally, particularly in low- and middle-income countries (LMICs), where limited data hinder comprehensive estimations (13).

In Ethiopia, neonatal hyperbilirubinemia is prevalent, and phototherapy serves as a primary treatment. However, the potential hematological side effects of phototherapy remain inadequately explored in this context. Existing literature highlights the global impact of hyperbilirubinemia, with sub-Saharan Africa and South Asia identified as primary contributors to severe cases. Despite this, there is a conspicuous lack of research within Ethiopia investigating the specific impact of phototherapy on hematological profile in newborns. This study aims to address this gap by determining the effect of phototherapy on the hematological profile of newborns with unconjugated hyperbilirubinemia at Saint Paul's Hospital Millennium Medical College Addis Ababa, Ethiopia.

1.2 statement of the problem

The Global Burden of Disease study places Severe Neonatal Jaundice (SNJ) in the top 5-10 causes of neonatal deaths in countries with the highest neonatal mortality rates (14). Previous efforts to estimate the global and regional burden of SNJ have encountered difficulties due to limited data. Bhutani et al. approximated a total of 481,000 cases of SNJ globally among term/near-term newborns, resulting in 114,000 deaths, with 75,000 survivors experiencing the development of kernicterus (15).

Available evidence points to the fact that low- and middle-income countries (LMICs) bear a disproportionate burden of severe neonatal hyperbilirubinemia (10, 15). To illustrate, a review regarding the global impact of hyperbilirubinemia, sub-Saharan Africa and South Asia were identified as the primary contributors to an estimated 1.1 million infants who develop severe jaundice globally each year (15). Furthermore, in Sub-Saharan Africa and South Asia, neonatal hyperbilirubinemia ranks as the seventh and eighth leading cause of infant mortality during the early neonatal period (i.e., 0-6 days), respectively (16).

In Ethiopia, neonatal hyperbilirubinemia carries a substantial burden, with a prevalence rate of 35.90%. This condition is notably linked to factors such as ABO blood incompatibility, Rh isoimmunization, neonatal sepsis, birth asphyxia, low birth weight, and prolonged labor (17). Phototherapy is presently the most widely utilized therapeutic approach for the treatment of neonatal hyperbilirubinemia. However, it's important to note that this treatment may have hematological side effects, including increase in leukocyte counts, anemia, and thrombocytopenia (4).

Phototherapy has been discovered to adversely affect different elements of the oxidant/antioxidant defense system in newborns, serving as a potential source of oxidative stress capable of harming cellular DNA. Furthermore, it has the capacity to disturb the pro-oxidant/antioxidant balance (PAB), resulting in a variety of symptoms and side effects (18).

These effects can lead to changes in peripheral blood counts. Phototherapy has the potential to impact the synthesis and release of cytokines, interleukins, and the immune mediator Tumor Necrosis Factor (TNF) from the skin's immune system (19). Neonates receiving phototherapy may have different leukocyte counts as a result of these modifications in immune response

modulation. When phototherapy is used in conjunction with hyperbilirubinemia, normal erythrocytes become more osmotically fragile, which can cause a range of changes in hemoglobin and other RBC characteristics (20).

To the best of the author's knowledge, there has been no research conducted within Ethiopia that examines the impact of phototherapy on hematological profiles and the varied findings in the literature highlight the crucial need for a comprehensive investigation into the hematological effects of phototherapy in newborns with unconjugated hyperbilirubinemia. Further investigations in this area could provide valuable insights for healthcare professionals, enhancing their awareness of the potential adverse effects of phototherapy. The purpose of this study was to examine whether phototherapy used to treat newborns with hyperbilirubinemia leads to changes in total and differential blood counts, hemoglobin levels, platelet count, erythrocyte counts and red cell indices.

1.3 significance of the study

The significance of this study extends beyond academic inquiry to directly benefit healthcare practitioners and most importantly, the neonatal population. By identifying and justifying potential risks associated with phototherapy, the study aims to enhance patient outcomes, contribute to the development of locally relevant clinical guidelines, and minimize treatment-related complications. Furthermore, this research addresses a critical knowledge gap in the context of neonatal care in Ethiopia. The findings are anticipated to provide valuable insights that will shape and direct healthcare practices, encouraging a more tailored use of phototherapy. In doing so, the study acts as a valuable reference for future investigations.

2. Literature review

The use of phototherapy as a treatment for newborns with unconjugated hyperbilirubinemia is a common practice in neonatal care. Several studies have investigated the effects of phototherapy on the hematological profile of newborns with unconjugated hyperbilirubinemia.

2.1 Effects of Phototherapy on RBC and WBC

In a cross-sectional study conducted in Nepal from 2019 to November 2020, researchers investigated the impact of phototherapy on the hematological profile of newborns with unconjugated hyperbilirubinemia. Analyzing complete blood counts in 120 infants before and after 48 hours of phototherapy, they found minimal change in mean total leukocyte count (16,580 cells/mm³ before, 16,860 cells/mm³ after). However, total lymphocyte count significantly increased (from 5,650 to 6,360 cells/mm³), while monocyte count decreased (from 730 to 530 cells/mm³). Although other hematological changes were not statistically significant, phototherapy had a significant impact on various parameters, emphasizing its influence on blood cell counts (21).

In a study conducted in Turkey from 2016 to 2017, investigating the impact of phototherapy on white blood cell parameters, significant changes were observed. Phototherapy led to a notable increase in eosinophil and basophil counts, as well as a significant decrease in leukocyte and neutrophil counts. However, there were no significant changes in monocyte and lymphocyte counts. The study also found a significant decrease in neutrophil volume values and a simultaneous increase in neutrophil scatter values after phototherapy, while neutrophil conductivity values remained unaffected. These findings emphasize specific alterations induced by phototherapy in the study population (22).

In a retrospective study conducted in Turkey in 2018, researchers evaluated 119 newborns treated with phototherapy for indirect hyperbilirubinemia. The study assessed the effects of phototherapy on peripheral blood cell counts and highlighted that phototherapy significantly impacted white blood cell (WBC) values after treatment, particularly decrease neutrophil/lymphocyte and lymphocyte/monocyte ratios. These findings suggested that

phototherapy might directly decrease cytokine and bilirubin levels, affecting peripheral blood cell counts (23).

A retrospective cross-sectional study conducted in Turkey in 2022, which involved 60 newborns with indirect hyperbilirubinemia, comprising 30 full-term and 30 preterm infants, revealed significant decreases in various hematological parameters such as WBC and RBC counts, Hgb, MCV, and RDW following phototherapy. Additionally, preterm infants exhibited further changes, including decreased lymphocyte counts and increased monocyte percentages. These findings underscore the importance of closely monitoring and managing hematological parameters during phototherapy in newborns with indirect hyperbilirubinemia (24).

In a longitudinal cohort study in Egypt from February to July 2022, focused on newborns with indirect hyperbilirubinemia undergoing phototherapy, significant decreases in hemoglobin concentration, RBC count, and platelet count were observed after 48 hours (p-value < 0.05) (25).

2.2 Effects of Phototherapy on platelet count

A cross-sectional study conducted in a Neonatology unit of a Hospital in Faisalabad, Pakistan, from January to September 2015, examining the impact of phototherapy on platelet count in hyperbilirubinemic neonates, 150 participants were involved. After 24 hours of phototherapy, 8.1% experienced severe thrombocytopenia ($<50 \times 10^9$/L), increasing to 18.4% after 48 hours and 33.3% after 72 hours. Phototherapy significantly reduced platelet counts, indicating a gradual rise in thrombocytopenia incidence without clinical bleeding manifestations (26).

In the prospective study conducted in Iran from 2007 to February 2008, the investigation focused on the influence of phototherapy on platelet count in full-term newborns with indirect hyperbilirubinemia. The study revealed a significant increase in the mean platelet count 287.83 K/UL before and 299.444 K/UL after phototherapy. The results indicated rise in platelet count following phototherapy, emphasizing the potential positive impact of extended treatment duration on platelet levels in newborns with indirect hyperbilirubinemia (27).

In a prospective cohort study conducted in India in 2014, the study found that the overall incidence of post-phototherapy related thrombocytopenia was 45.6%. Among the affected neonates, 66% experienced mild thrombocytopenia, 21.3% had moderate thrombocytopenia, and 12.8% exhibited severe thrombocytopenia. These findings highlight the relatively high

occurrence of thrombocytopenia in newborns undergoing phototherapy for indirect hyperbilirubinemia and emphasize the need for vigilant monitoring and management of platelet levels during such treatment (28).

In a longitudinal cohort study in Egypt from February to July 2022, focused on newborns with indirect hyperbilirubinemia undergoing phototherapy, mild thrombocytopenia was experienced by 13.3%, and 1.7% exhibited moderate thrombocytopenia. Full-term newborns showed a significant decrease in RBCs and hemoglobin concentration (25).

The literature cited above presents a range of findings that highlight the necessity of conducting a thorough examination of the hematological consequences of phototherapy in newborns with unconjugated hyperbilirubinemia. This work is of utmost importance since it attempts to fill in the knowledge gaps regarding phototherapy's effects on blood parameters by providing a more nuanced view of the variances seen in various groups. Through a methodical analysis and synthesis of these inconsistent findings, the study aims to offer a coherent and empirically supported framework. The study's importance ultimately rests in its ability to inform clinical procedures and offer insightful information to medical professionals, guaranteeing that newborns receiving phototherapy receive the best care possible that is customized to their unique hematological reactions (27).

3. Objectives

3.1 General objective

To assess the effect of phototherapy on hematological profile of newborns with unconjugated hyperbilirubinemia at Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia from February to April 2024.

3.2 Specific objectives

- To determine the effect of phototherapy on hematological profile of newborns with unconjugated hyperbilirubinemia before and after phototherapy.
- To determine the relationship between the duration of phototherapy and its effect on observed hematological effect among newborns with unconjugated hyperbilirubinemia.

4. Materials and methods

4.1. Study area

The study took place at SPHMMC, found in Addis Ababa, Ethiopia, which serves as the capital city of the country. SPHMMC claims a workforce exceeding 2800 individuals encompassing clinical, academic, administrative, and support roles. The institution plays a vital role in medical and nursing education, conducting both basic and applied research, and offering specialized medical services to patients referred from across the nation. Although equipped to accommodate over 700 inpatient beds, the hospital attends to an average of 1200 emergency and outpatient cases daily (29).

4.2. Study period

The study was conducted from February to April 2024 at Saint Paul's Hospital Millennium Medical College.

4.3. Study design

Institutional based cross-sectional study was conducted at Saint Paul's Hospital Millennium Medical College. Participants were categorized based on the duration of phototherapy they received: 24 hours, 48 hours, or 72 hours. This design enabled the assessment of changes in hematological profiles and bilirubin levels before and after phototherapy within each specific duration category, rather than tracking changes across all three time points for each newborn. This approach allowed for a clear analysis of the impact of varying phototherapy durations on the hematological profiles of the newborns in the study.

4.4. Population

4.4.1. Source of population

The source population was all newborns with unconjugated hyperbilirubinemia who were attending Saint Paul's Hospital Millennium Medical College during the study period.

4.4.2. Study population

The study population was all eligible newborns with unconjugated hyperbilirubinemia who were admitted to Saint Paul's Hospital Millennium Medical College and undergo phototherapy as part of their treatment during the study period.

4.5. Inclusion and exclusion criteria

4.5.1 Inclusion criteria

All newborns with unconjugated hyperbilirubinemia who underwent phototherapy as a treatment were included in the study. Furthermore, newborns who had not received treatment from other hospitals and whose parents provided informed assent for participation in the study were considered for inclusion.

5.5.2. Exclusion criteria

Exclusion criteria for the effect of phototherapy determination in hematological profile were;-

- Those Newborns who undergo exchange transfusion.
- Newborns with contraindications for treatment with blue light irradiation.
- Newborns with serious infections and diseases.

4.6. Variables of the study

4.6.1. Dependent variable

- Hematological profile

4.6.2. Independent variable

- Duration of phototherapy
- Gestational age Category

4.7. Sample size determination and sampling technique

4.7.1. Sample size determination

The sample size of the study was calculated by using the mean value of the effect of phototherapy on blood count from the study conducted in Egypt where 13.3% of newborns undergoing phototherapy experienced mild thrombocytopenia, (25). To determine the required sample size for the study a single population proportion formula was used as denoted bellow.

$$n = \frac{Z\alpha/2^2 \, P(1-P)}{d^2}$$

N= n+10 % of n

Where:-

- N= total minimum sample size
- d= Margin of error between the sample and the population (d=5%)
- n = Sample size
- p= estimated population proportion (13.3%)
- Z α/2 = 95% confident interval from the normal table for a given value (1.96)
- n = $(1.96)^2$*0.133(1-0.133)/($0.05)^2$ =177

N = $(1.96)^2$ x 0.133(1-0.133)/ $(0.05)^2$ + it's 10% =177+18= 195. These were the minimum sample size.

4.7.2. Sampling technique

Convenient sampling technique was used at Saint Paul's hospital millennium medical college.

4.8. Measurement and data collection

The study was begun by obtaining informed assent from parents providing detailed information on the study's purpose and procedures to ensure their active participation. Subsequently, a team of trained data collectors was precisely recorded essential information, including the gestational age, age at admission, birth weight, sex, and bilirubin levels of the newborns that were diagnosed with unconjugated hyperbillirubinemia and was underwent phototherapy treatment from patient chart using a clear checklist as a data collection tool. About 2 ml of venous blood was collected from selected newborns by using EDTA blood collection tube, both before and after phototherapy, employing established techniques by assigned phlebotomists in the NICU. To ensure appropriate cell suspension and prevent clumping, each blood sample was mixed with a diluent. Subsequently, these prepared samples underwent analysis using the Mindray BC-6800 plus Auto Hematology Analyzer in the hematology Laboratory of SPHMMC.

A complete pre-phototherapy and post-phototherapy hematological profile was recorded encompassing critical parameters such as RBC count, WBC count, Hgb concentration, HCT level, platelet count, MPV, MCV, MCH, MCHC, RDW and WBC differential count. Bilirubin levels were measured both before and immediately after phototherapy, and data collector was carefully noted the duration of phototherapy administered to each newborn throughout the data collection process.

4.8.1 Venous blood collection procedure

1. Gathered supplies, including sterile gloves, alcohol swabs or antiseptic solution, tourniquet, needle (typically a butterfly needle), syringe, blood collection tubes, gauze pads, adhesive bandage or tape, and sharps disposal container.
2. Ensured a calm environment by minimizing noise and movement, and having a parent or caregiver present to help soothe the baby.
3. Washed hands thoroughly with soap and water, and put on sterile gloves.
4. Positioned the newborn comfortably and securely, possibly swaddling the baby, and had an assistant hold the baby if necessary.
5. Selected the venipuncture site, commonly the veins in the hands, feet, or antecubital fossa (inside of the elbow), and applied a tourniquet gently above the chosen site to engorge the veins.
6. Cleaned the site thoroughly with an alcohol swab or antiseptic solution, and allowed the area to air dry completely.
7. Held the needle at a 15-30 degree angle to the skin, and inserted it smoothly into the vein with the bevel facing up, securing the wings if using a butterfly needle.
8. Attached the syringe to the needle, drew 2-3 ml of blood quickly and smoothly, and released the tourniquet before removing the needle.
9. Gently withdrew the needle from the vein, immediately applying pressure to the puncture site with a gauze pad to stop bleeding.
10. Once the bleeding had stopped, applied an adhesive bandage or taped a piece of gauze to the site.
11. Disposed of the needle and any other sharps in a designated sharps container, and disposed of gloves and other non-reusable materials properly.
12. Observed the baby for any signs of distress or adverse reactions, providing comfort and reassurance to the infant and caregiver.
13. Recorded the procedure details, including the time, site of venipuncture, volume of blood collected, and any observations during and after the procedure.

4.8.2 Principle and procedure of Mindray BC-6800plus auto hematology analyzer

The Mindray BC-6800plus auto hematology analyzer employs multiple principles for comprehensive blood analysis:

1. Electrical Impedance (Coulter Principle): It accurately counts and sizes red blood cells (RBCs) and platelets (PLTs) by measuring changes in electrical impedance as blood cells pass through an aperture, ensuring precise quantification and sizing.
2. Flow Cytometer: The analyzer uses flow cytometer to differentiate and count white blood cells (WBCs) with high accuracy, utilizing fluorescent dyes and laser-based analysis for WBC type identification.
3. Hemoglobin Measurement: Hemoglobin concentration is measured photometrically, ensuring precise hemoglobin level assessment.

Procedure

1. Mixed the sample thoroughly, either by shaking a capped micro whole blood sample tube or an evacuated collection tube.
2. Placed the sample tube in the appropriate position in the sample compartment, ensuring the correct tube position switch setting.
3. Pressed the [Run] key to start sample analysis, allowing the sample probe to automatically aspirate the sample.
4. After aspiration, removed the sample safely once the compartment opened.
5. The analyzer ran the sample, and the indicator flickered green during the process.
6. When analysis completed, the indicator returned to "Ready" status, displaying the results, histograms, scatter grams, and any flags on the screen.

4.8.3 Principle of Bilirubin Level Determination on Cobas chemistry 6000 analyzer

1. **Sample Preparation:**
    - Blood is collected from the patient, typically in a serum separator tube (SST) or plasma collection tube.
    - The sample is centrifuged to separate the serum or plasma from blood cells.
2. **Chemical Reaction:**
    - The Cobas 6000 uses a photometric method to determine bilirubin levels.
    - In the presence of a specific reagent, bilirubin reacts to form a colored complex.
    - For total bilirubin, the reagent contains a diazo compound that reacts with both conjugated (direct) and unconjugated (indirect) bilirubin to form azobilirubin, a colored compound.
    - For direct bilirubin (conjugated bilirubin), a separate reaction involving only conjugated bilirubin is performed.
3. **Measurement:**
    - The sample with the reacted bilirubin is placed in the reaction cuvette.
    - The Cobas 6000 analyzer measures the absorbance of the colored complex at specific wavelengths using a photometer.
    - The intensity of the color is proportional to the concentration of bilirubin in the sample.
4. **Calculation:**
    - The absorbance readings are compared against a calibration curve established using known standards.
    - The analyzer calculates the bilirubin concentration based on the calibration curve and the absorbance values obtained from the patient sample.
5. **Results:**
    - The Cobas 6000 provides the concentration of total bilirubin and, if tested, direct bilirubin.
    - The results are typically reported in milligrams per deciliter (mg/dL) or micromoles per liter (µmol/L).

4.9 Data Quality Control and Quality Assurance

The reliability of the study findings was ensured by implementing quality control measures throughout the entire laboratory process. All materials, equipment, and procedures were thoroughly controlled. The data collection tool was pre-tested to ensure its accuracy and consistency before actual data collection began. Additionally, advisors provided daily feedback and corrections to the data collectors. The completeness, accuracy, and clarity of the collected data were regularly and carefully checked.

Before the commencement of actual data collection, a pretest was carried out on 5% of the total study population other than SPHMMC. A comprehensive one-day training session was provided to all data collectors to ensure uniformity and accuracy in data collection procedures. On a daily basis, each checklist was cross-checked to verify completeness and eliminate redundancy. Throughout the data collection period, supervisors was closely monitored the data collection process, ensuring the integrity and reliability of the collected data. A pre-analytical, analytical and post-analytical stage of quality assurance that was incorporated in standard operating procedures was strictly followed.

4.9.1 Pre Analytical Phase

During the pre-analytical phase, Specimens were meticulously labeled Medical Record Numbers (MRNs), and dates to avoid any identification errors. Appropriate volume of blood and anticoagulant was used to maintain the specimen's quality.

Careful attention was given to checking for hemolysis, clotting, and specimen contamination, and a waiting period of 10 to 15 minutes observed to stabilize anticoagulants with the blood.

4.9.2 Analytical phase

During Analytical phase of quality control program routine checks of instruments and reagents, with control samples run at defined intervals for monitoring. The analytical process was involving a thorough check for any issues related to the instrument, reagents, or sample preparation. Every day before the sample was run, low; medium and high control reagent were used for Mindray BC-6800plus auto hematology analyzer to maintain the reagents quality and preventive maintenance.

Controls for the hematology analyzer were established in the absence of commercial controls. A blood sample from a healthy individual was served as the normal control, while a low control was created by centrifuging a normal blood sample to obtain reduced plasma. For the high control, the cellular portion of a normal blood sample was used.

4.9.3 Post analytical Phase

In the post-analytical stage, results for newborns were carefully verified for accuracy before release, and correlations with clinical information were made to ensure relevance and consistency. Reference ranges appropriate for newborns were included, and results were reported clearly, encompassing any abnormal findings or flags. The entire process was precisely documented, including interpretations and correlations with clinical information.

4.10. Data analysis and interpretation

The data was precisely processed, involving data entry, coding, cleaning, sorting, and analysis, utilizing SPSS statistical software version 25. The study findings were underwent thorough checks for frequencies, accuracy, consistencies, identification of missed values, and variable assessments manually. Any identified errors were promptly corrected. Categorical data were summarized using frequency and percentage values. For descriptive statistics, mean ± standard deviation was reported. To evaluate the differences in hematological parameters before and after phototherapy, a paired sample t-test was conducted. A p-value of less than 0.05 was considered to indicate statistical significance. Final, results of this study was present in the form of tables, figures, and texts as appropriate.

4.11 Operational definition

- **Newborns:** Infants within the first 28 days of life (30).
- **Gestational Age:** the duration of pregnancy counted from the first day of the last menstrual period to the time of birth, typically expressed in completed weeks (31).
- **Preterm:** A "preterm" newborn, as per this research, is an infant born before the completion of 37 weeks of gestation (30).
- **Term:** In this study, "term" infants are those born at or after 37 weeks of gestation but before the beginning of the 42nd week (31).

- **Unconjugated Hyperbilirubinemia:** A medical condition characterized by elevated levels of unconjugated (indirect) bilirubin in the bloodstream (4).
- **Hematological Profile**: A hematological profile refers to a set of blood tests that provides information about the various components of blood and their health status. Parameters such as RBC count, WBC count, Hgb concentration, HCT level, platelet count, MPV, MCV, MCH, MCHC, RDW and WBC differential count.

4.12. Ethical consideration

Ethical approval obtained from the Research and Ethics Committee of the Medical Laboratory Sciences Department, College of Health Sciences, Addis Ababa University (DRERC/747/24/MLS/), and Institutional Review Board of SPHMMC (PM23/1030/2024). Informed written assent was obtained from parents, with a clear explanation of the research objectives. Participation in the study was voluntary. To safeguard data confidentiality, study subjects were identified using codes, ensuring unauthorized access prevention.

4.13. Result dissemination plan

The outcomes of this study will be shared with the Department of Medical Laboratory Science at Addis Ababa University and Saint Paul Hospital Millennium Medical College. Furthermore, the research findings will be disseminated to pertinent healthcare planners and individuals seeking this information as a valuable reference for their own studies. In addition to these vital steps, commitment will be made to presenting the findings at both national and international conferences, as well as publishing them in reputable journals, ensuring that the knowledge gained is shared widely and contributes to the broader scientific community.

5. Result

5.1Socio-demographic and Clinical Characteristics of Newborns Undergoing Phototherapy

There were 195 Newborn participants in the study. It was observed that 77.9% (152/195) of the newborn participants were male. The age range at admission was 1 to 9 days, with a mean age of 2.64 days and standard deviation of 1.538 days. Regarding gestational age, 60.0% (117/195) were classified as term infants. The majority of newborns, 67.2% (131/195), weighed more than 2500g at birth. The majority of newborns were delivered vaginally, accounting for 77.9% (91/195) of the total participants. Additionally, 55.4% (108/195) of patients underwent phototherapy for 48 hours duration, (Table 1).

Table 1:- Socio-demographic data of Newborns studied at Saint Paul's Hospital Millennium Medical College from February to April 2024 (n = 195)

Parameter		No (%)
Sex	Male	152(77.9%)
	Female	43(22.1%)
Mode of delivery	Normal vaginal delivery	152(77.9%)
	C-section	43(22.1%)
Birth Weight in gram	> 2,500	131(67.2%)
	≤ 2,500	64 (32.8%)
Gestational Age Category	Preterm	78 (40.0%)
	Term	117 (60.0%)
Duration of Phototherapy (hours)	24	65 (33.3%)
	48	108 (55.4%)
	72	22(11.3%)

5.2 Effect of Phototherapy on Hematological Profile and Bilirubin level in newborns

Phototherapy significantly reduces bilirubin levels in newborns with unconjugated hyperbilirubinemia, decreasing from a mean of 11.85 mg/dl to 3.66 mg/dl ($p < 0.001$). It also lowers RBC count from 4.74 to 4.43 x 10^12 / L ($p < 0.001$), Hgb levels from 16.81 to 16.20 g/dl ($p < 0.001$), and HCT from 45.17% to 44.19% ($p = 0.003$). WBC count increases from 9.90 to 11.02 x 10^3 / mm^3 ($p < 0.001$), with lymphocyte percentage rising from 27.79% to 30.13% ($p < 0.001$) and monocyte percentage decreasing from 8.68% to 7.12% ($p < 0.001$). Platelet count and MCHC also decrease significantly, (Table 2).

Table 2:- Hematological profile and bilirubin level before Phototherapy and after Phototherapy for all studied newborns at Saint Paul's Hospital Millennium Medical College from February to April 2024 (n = 195)

Parameter	Before PT (Mean ± SD)	After PT (Mean ± SD)	p-value
Bilirubin (mg/dl)	11.85 ± 5.31	3.66 ± 2.37	< 0.001
RBC (10^12 / L)	4.74 ±0.89	4.43 ± 0.76	< 0.001
Hgb (g/L)	168.1 ± 3.37	162.0 ± 3.23	< 0.001
HCT (%)	45.17 ± 9.49	44.19 ± 8.95	0.003
WBC (10^9 / L)	9.90 ± 4.39	11.02 ± 4.76	< 0.001
Lymphocyte (%)	27.79 ± 12.17	30.13 ± 11.92	< 0.001
Monocyte (%)	8.68 ± 4.86	7.12 ± 5.05	< 0.001
Eosinophil (%)	2.41 ± 6.14	2.00 ± 3.22	0.368
Neutrophil (%)	60.52 ± 14.51	60.77 ± 13.64	0.652
Basophil (%)	0.21 ± 0.49	0.23 ± .49	0.131
Platelet (10^9 / L)	220.52 ± 81.53	207.72 ± 78.41	< 0.001
MPV (fl)	9.68 ± 1.53	9.74 ± 1.13	0.410
MCV (fl)	95.71 ± 12.05	95.92 ± 7.42	0.768
MCH (pg)	35.50 ± 5.21	35.37 ± 4.07	0.587
MCHC (g/L)	372.2 ± 4.30	365.6 ± 1.42	0.022
RDW (%)	16.16 ± 2.18	15.83 ± 1.61	0.005

NB: - RBC = Red Blood Cell, Hgb= Hemoglobin, HCT= Hematocrit, WBC= White Blood Cell, MPV= Mean Platelet Volume, MCV=Mean Corpuscular Volume, MCH= Mean Corpuscular Hemoglobin, MCHC= Mean Corpuscular Hemoglobin Concentration, RDW = Red Cell Distribution Width, PT= Phototherapy

5.3 Effect of Phototherapy on Hematological profile and Bilirubin level in Term Newborns

In term newborns (n=117), phototherapy (PT) effectively reduces bilirubin levels ($t = -18.628$, $p < 0.001$). Significant decreases are observed in RBC count ($t = -8.703$, $p < 0.001$), Hgb ($t = -4.531$, $p < 0.001$), and platelet count ($t = -11.015$, $p < 0.001$). WBC count ($t = 3.195$, $p = 0.002$) and lymphocyte count ($t = 7.713$, $p < 0.001$) increase significantly, while RDW decreases ($t = -2.517$, $p = 0.013$). HCT, Eosinophil, Neutrophil, Basophil counts, MCV, MCH, and MCHC show no significant changes, (Table 3).

Table 3:- Effect of Phototherapy on Hematological profile and bilirubin level in Term Newborns at Saint Paul's Hospital Millennium Medical College from February to April 2024 (n = 117)

Parameters	Difference (After –Before) (Mean)	t-value from paired-t test	P-value
Bilirubin (mg/dl)	-7.861578	-18.628	< 0.001
RBC (10^12 / L)	-0.286692	-8.703	< 0.001
Hgb (g/L)	-0.649829	-4.531	< 0.001
HCT (%)	-0.855556	-1.737	0.085
WBC (10^9 / L)	1.338803	3.195	0.002
Lymphocyte (%)	2.620256	7.713	< 0.001
Monocyte (%)	-1.406239	-5.897	< 0.001
Eosinophil (%)	-0.002991	-0.007	0.994
Neutrophil (%)	-0.209402	-.372	0.711
Basophil (%)	0.041026	2.008	0.047
Platelet (10^9 / L)	-12.155	-11.015	< 0.001
MPV (fl)	0.057265	0.698	0.487
MCV (fl)	0.197436	0.231	0.818
MCH (pg)	0.120513	0.318	0.751
MCHC (g/L)	-0.888034	-1.866	0.065
RDW (%)	-0.448718	-2.517	0.013

NB: - RBC = Red Blood Cell, Hgb= Hemoglobin, HCT= Hematocrit, WBC= White Blood Cell, MPV= Mean Platelet Volume, MCV=Mean Corpuscular Volume, MCH= Mean Corpuscular Hemoglobin, MCHC= Mean Corpuscular Hemoglobin Concentration, RDW = Red Cell Distribution Width, PT= Phototherapy

5.4 Effect of Phototherapy on Hematological Profile and Bilirubin Level in Preterm Newborns

In preterm newborns (n= 78), phototherapy significantly reduces bilirubin levels ($t = -21.030$, $p < 0.001$). Significant reductions are observed in RBC count ($t = -4.184$, $p < 0.001$), Hgb ($t = -4.138$, $p < 0.001$), HCT ($t = -3.190$, $p = 0.002$), MCH ($t = -3.840$, $p < 0.001$) and MCHC ($t = -4.648$, $p < 0.001$). Platelet count also decreases significantly ($t = -4.301$, $p < 0.001$). Conversely, WBC count ($t = 2.356$, $p = 0.021$) and lymphocyte count ($t = 6.633$, $p < 0.001$) increase significantly post-treatment. Eosinophil, neutrophil, basophil counts, MPV, MCV, and RDW show no significant changes, (Table 4).

Table 4:- Effect of Phototherapy on Hematological profile and bilirubin level in Pre Term Newborns at Saint Paul's Hospital Millennium Medical College from February to April 2024 (n = 78)

Parameters	Difference (After – Before) (Mean)	t-value from paired-t test	P- value
Bilirubin (mg/dl)	-8.681253	-21.030	< 0.001
RBC (10^12 / L)	-0.333205	-4.184	< 0.001
Hgb (g/L)	-0.556154	-4.138	< 0.001
HCT (%)	-1.146282	-3.190	0.002
WBC (10^9 / L)	0.796282	2.356	0.021
Lymphocyte (%)	1.902564	6.633	< 0.001
Monocyte (%)	-1.798718	-8.183	< 0.001
Eosinophil (%)	-1.033333	-1.070	0.288
Neutrophil (%)	0.934615	0.864	0.390
Basophil (%)	-13.769	0.046	0.963
Platelet (10^9 / L)	0.001282	-4.301	< 0.001
MPV (fl)	0.066667	0.482	0.631
MCV (fl)	0.226923	0.184	0.854
MCH (pg)	-0.498718	-3.840	< 0.001
MCHC (g/L)	-0.324359	-4.648	< 0.001

NB: - RBC = Red Blood Cell, Hgb= Hemoglobin, HCT= Hematocrit, WBC= White Blood Cell, MPV= Mean Platelet Volume, MCV=Mean Corpuscular Volume, MCH= Mean Corpuscular Hemoglobin, MCHC= Mean Corpuscular Hemoglobin Concentration, RDW = Red Cell Distribution Width, PT= Phototherapy

5.5 Effect of Phototherapy Duration on Hematological Profiles and Bilirubin Level in Newborns

Participants were categorized based on the duration of phototherapy they received: 24 hours, 48 hours, or 72 hours.

Those who had 24 hours of phototherapy (n=65), significant reductions in bilirubin levels ($p < 0.001$), RBC count ($p < 0.001$), Hgb levels ($p < 0.001$), and HCT levels ($p < 0.01$) indicate effective treatment of hyperbilirubinemia and a suppressive effect on erythropoiesis. There are significant increases in white blood cell count ($p < 0.01$) and lymphocyte percentage ($p < 0.001$), while monocyte percentage decreases significantly ($p < 0.001$).

In those who had 48 hours of phototherapy(n=108), the reductions in bilirubin levels ($p < 0.001$), RBC count ($p < 0.001$), Hgb levels ($p < 0.001$), and HCT levels ($p < 0.01$) persist, with continued increases in white blood cell count ($p < 0.01$) and lymphocyte percentage ($p < 0.001$), and a further decrease in monocyte percentage ($p < 0.001$).

The rest of newborns after 72 hours of phototherapy (n=22), bilirubin levels continue to decrease significantly ($p < 0.001$). The increase in lymphocyte percentage remains significant ($p < 0.001$), but other parameters such as RBC count, Hgb levels, and HCT levels do not show significant changes. Monocyte percentage shows no significant change ($p = 0.461$), indicating a diminishing impact on this parameter with longer treatment durations, (Table 5).

Table 5:- Comparison of hematological profile and bilirubin levels in Newborns before and after 24, 48 and 72 hour of phototherapy.at Saint Paul's Hospital Millennium Medical College from February to April 2024 (n = 195)

Parameter	Duration	Mean Difference (After – Before)	t-value	p-value
Bilirubin (mg/dL)	24-hour	-6.879675	-19.293	< 0.001
	48-hour	-8.559705	-23.431	< 0.001
	72-hour	-10.241605	-6.403	< 0.001
RBC (10^12 / L)	24-hour	-0.261077	-8.717	< 0.001
	48-hour	-0.355213	-5.788	< 0.001
	72-hour	-0.190909	-1.841	0.080
Hgb (g/dl)	24-hour	-0.527077	-4.740	< 0.001
	48-hour	-0.746481	-4.879	< 0.001
	72-hour	-0.205909	-0.571	0.574
HCT (%)	24-hour	-0.986154	-2.659	0.010
	48-hour	-1.308426	-2.690	0.008
	72-hour	0.722727	.591	0.561
WBC(10^9 / L)	24-hour	0.862154	2.616	0.011
	48-hour	1.417407	3.190	0.002
	72-hour	0.437727	0.521	0.608
Lymphocyte (%)	24-hour	1.890769	5.491	0.000
	48-hour	2.398796	7.365	0.000
	72-hour	3.318182	3.919	0.001
Monocyte (%)	24-hour	-1.781538	-6.971	< 0.001
	48-hour	-1.649352	-7.441	< 0.001
	72-hour	-.495455	-.752	0.461
Platelet (10^9 / L)	24-hour	-12.923	-10.744	< 0.001
	48-hour	-12.390	-5.014	< 0.001
	72-hour	-14.455	-7.908	< 0.001
MCHC (g/L)	24-hour	-.361538	-5.225	< 0.001
	48-hour	-.885185	-1.716	0.089
	72-hour	-0.459091	-3.495	0.002
RDW %	24-hour	-0.240000	-5.624	< 0.001
	48-hour	-0.496296	-2.574	0.011
	72-hour	0.172727	0.423	0.676

6. Discussion

Phototherapy, a standard treatment for neonatal jaundice, effectively reduces bilirubin levels in newborns. However, beyond its primary aim of bilirubin reduction, phototherapy elicits complex physiological responses, influencing various hematological parameters and modulating the immune system.

In this study, a significant decrease in bilirubin levels after phototherapy was observed in both term ($p < 0.001$) and preterm newborns ($p < 0.001$). This finding is consistent with Eyada I. et al., and Atia T. et al. who also reported a significant reduction in bilirubin levels after phototherapy ($p < 0.01$) (32, 33). Such consistent results suggesting that phototherapy effectively reduces neonatal jaundice by converting bilirubin into water-soluble forms using visible light, aiding its elimination (10).

Significant decreases in RBC count ($p < 0.001$) and Hgb ($p < 0.001$) were observed post-treatment in term newborns. Similarly, preterm newborns showed reductions in RBC count ($p < 0.001$), Hgb ($p < 0.001$), and HCT ($p = 0.002$) levels post-phototherapy. These findings align with those of Moured M. et al., who found significant decreases in mean Hgb concentration and RBC count after 48 hours of phototherapy ($p < 0.05$) (25), Fathima H. et al. (24) also reported significant reductions in mean RBC counts and mean Hgb levels after phototherapy in term newborns indicating phototherapy, increases the osmotic fragility of normal erythrocytes this increased fragility can cause changes in hemoglobin and other RBC characteristics.

However, a study conducted by Timilsina M. et al (21) indicated that phototherapy did not cause significant changes in RBC count and Hgb levels, suggesting variability in hematological responses to phototherapy among different populations. The variability of results observed in different studies may arise from various factors, such as differences in phototherapy duration, gestational age, and underlying conditions.

After phototherapy significant increases in WBC count ($p = 0.002$) and lymphocyte count ($p < 0.001$) was observed in both term and preterm newborns. This finding is consistent with Moured M. et al., who also reported increases in WBC and lymphocyte counts following phototherapy suggesting potential immune system activation (25). Mrkaić L. et al. noted that phototherapy

might heighten the risk of infection due to a rise in WBC counts and delayed chemo-luminescence response of phagocytes, though these effects were temporary (34). However, Kurt A. et al. and Eyada I. et al. reported decreases in WBC counts post-phototherapy (23, 32), highlighting variability in hematological responses across studies. Karabayir N. et al. found no significant changes in lymphocyte counts after 48 hours of phototherapy (35). Phototherapy has been shown to modify the synthesis and release of cytokines, interleukins, and TNF immune mediators from the skin's immune system. Newborns undergoing phototherapy may exhibit alterations in leukocyte counts due to these modifications in immune response (12).

The study found a significant decrease in platelet count after phototherapy ($t = -11.015$, $p < 0.001$) in both term and preterm infants. This is consistent with studies by Fatima H. et al., who reported significant platelet reductions after phototherapy (24). In a study conducted by Sajid A. et al., phototherapy significantly lowered platelet counts in hyperbilirubinemic newborns, with severe thrombocytopenia rates increasing from 8.1% after 24 hours to 33.3% after 72 hours without clinical bleeding manifestations (26). Similarly, Khera S. and Gupta R. observed a 45.6% incidence of post-phototherapy thrombocytopenia, emphasizing the importance of careful platelet monitoring during treatment (28) with the decline attributed to photochemical reactions and direct platelet damage induced by phototherapy's ultraviolet light (28, 36). However, Monsef A. and Eghbalian F. reported a significant increase in mean platelet count after 48-72 hours of phototherapy in full-term newborns with indirect hyperbilirubinemia, suggesting a potential positive impact of extended treatment on platelet levels (27).

No significant changes were observed in eosinophil, neutrophil, and basophil counts after phototherapy in term or preterm newborns. This aligns with findings from Fatima H. et al. and Timilsina M. et al., who also reported no changes in these counts after phototherapy (21, 24). However, a study in Turkey reported significant changes in white blood cell parameters, including increased eosinophil and basophil counts, after phototherapy (35). Aydin B. et al. found a low eosinophil count with high bilirubin suppression of vascular cell adhesion molecule-1 before phototherapy, emphasizing bilirubin's role in immune modulation (37).

MCV and MCH remained unchanged post-treatment in both term and preterm newborns, suggesting stability in RBC morphology. However, mean MCHC and RDW exhibited a significant decrease after phototherapy in term newborns ($p = 0.013$). Fatima H. et al. observed

similar decreases in leukocyte and erythrocyte counts, Hgb, MCV, and RDW values in term newborns after phototherapy (24). Timilsina M. found an increase in MCH post-phototherapy, attributing this to hemolysis caused by the treatment (21). These varied findings highlight the complexity of phototherapy's impact on hematological profile.

Post-phototherapy, significant decreases in monocyte percentage were observed in both term and preterm newborns (term: $t = -5.897$, $p < 0.001$; preterm: $t = -6.971$, $p < 0.001$), suggesting modulation of the immune response. This finding aligns with Timilsina M et al., who observed decreased monocyte counts after phototherapy (21). However, Fatima H. et al. Reported increased monocyte percentages after phototherapy (24). The observed variability in immune parameters post-phototherapy underscores the complex interplay between phototherapy and the immune system,

The study also found phototherapy duration significantly reduced bilirubin levels after 24, 48, and 72 hours ($p < 0.001$). RBC counts, hemoglobin levels, and hematocrit decreased significantly after 24 and 48 hours ($p < 0.01$) but not after 72 hours, indicating a diminishing effect over time. WBC counts increased significantly after 24 and 48 hours ($p < 0.01$) but not after 72 hours. Lymphocyte percentages increased consistently ($p < 0.001$), while monocyte percentages decreased significantly at 24 and 48 hours ($p < 0.001$) but not at 72 hours. Eosinophil percentages showed no significant changes, and other parameters exhibited heterogeneous changes without consistent patterns. In line with the study findings, Sajid A, et al. and. Shah MH, Vedula R and Roshan R. et al. reported a direct relationship between longer phototherapy durations and increased severe thrombocytopenia (26, 38). One potential explanation for the observed differences in effect of phototherapy in platelet counts could be the variation in treatment protocols, including differences in the duration and intensity of phototherapy administered (39). These differences in findings highlight the need for further research to understand the variable effect of phototherapy duration on hematological profiles.

7. Strength and limitation of the study

7.1 Strength of the study

Strengths of the study include its comprehensive analysis of the effects of phototherapy on hematological profile in both term and preterm newborns. By separately analyzing the effects in each group, the study provides an understanding of phototherapy effects on hematological profiles in different newborn populations. Additionally, the study highlights the influence of phototherapy duration on hematological profile offering valuable insights for optimizing treatment protocols.

7.1 Limitation of the study

Limitation of the study lies in the cross-sectional design employed. Specifically, the reliance on a single time point for data collection may constrain the analysis of dynamic changes in hematological profile over the duration of phototherapy treatment. Consequently, the study may not capture the full spectrum of fluctuations in these parameters, potentially limiting the depth of understanding regarding the effects of phototherapy on newborns with hyperbilirubinemia.

8. Conclusion and Recommendation

8.1 Conclusion

The study found significant changes in selected hematological profiles before and after phototherapy in newborns with unconjugated hyperbilirubinemia, although these changes were within normal clinical ranges and not clinically significant. There were notable decreases in bilirubin levels, alongside reductions in RBC count, Hgb levels, HCT, RDW, monocyte percentage, and platelet count. Additionally, significant increases in WBC count and lymphocyte percentage were observed post-phototherapy. These findings highlight the effectiveness of phototherapy in reducing bilirubin levels and its impact on various hematological parameters, even though these changes were minimal and within the normal range. The results contribute to the understanding of how phototherapy affects hematological profiles in newborns with hyperbilirubinemia without leading to clinically significant alterations.

8.2 Recommendation

To optimize the management of newborn hyperbilirubinemia through phototherapy, it is recommended that clinicians routinely monitor hematological profiles, including RBC count, Hgb levels, WBC count, lymphocyte counts, monocyte counts, and platelet counts, even though the observed changes are not clinically significant. This monitoring ensures early detection of any potential adverse changes. Further prospective clinical research is necessary to validate these findings and explore any long-term effects. Establishing standardized guidelines for phototherapy duration and intensity is crucial. Establishing standardized guidelines for phototherapy duration and intensity, providing comprehensive training for healthcare professionals, and educating parents about potential hematological changes are crucial. An integrated care approach involving neonatologists, pediatricians, and hematologists is essential, alongside the promotion of advanced phototherapy technologies for precise treatment control.

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9. Annex

Annex I laboratory analysis

In the proposed research study, the Mindray BC-6800plus automated hematology analyzer will play a pivotal role in the data collection process. This sophisticated instrument combines advanced technologies to accurately analyze blood samples and assess hematological parameters, essential for evaluating the pre- and post-phototherapy hematological profiles of newborns with unconjugated hyperbilirubinemia.

Principle

The Mindray BC-6800plus auto hematology analyzer employs multiple principles for comprehensive blood analysis:

4. Electrical Impedance (Coulter Principle): It accurately counts and sizes red blood cells (RBCs) and platelets (PLTs) by measuring changes in electrical impedance as blood cells pass through an aperture, ensuring precise quantification and sizing.

5. Flow Cytometer: The analyzer uses flow cytometer to differentiate and count white blood cells (WBCs) with high accuracy, utilizing fluorescent dyes and laser-based analysis for WBC type identification.

6. Hemoglobin Measurement: Hemoglobin concentration is measured photometrically, ensuring precise hemoglobin level assessment.

Procedure

1. Mix the sample.
   - If you are running a whole blood sample collected in an evacuated collection tube, mix the sample thoroughly.
   - If you are running a micro whole blood sample collected in an anticoagulant tube or a centrifugal tube, cap the tube and shake the capped tube to mix it thoroughly.
2. Place the sample tube into the appropriate tube position in the sample compartment.

- If you are running a whole blood sample collected in an evacuated collection tube, make sure the tube position switch is at the PD/Micro WB tube position side. Then place the whole blood sample tube into the WB tube position.
- If you are running a micro whole blood sample collected in an anticoagulant tube or a centrifugal tube, make sure the tube position switch is at the WB tube position side. Then place the micro whole blood sample tube uncapped into the PD/Micro WB tube position.

3. Press the [Run] key on the analyzer front cover to start sample analysis.
   - The sample compartment closes, and the sample probe automatically aspirates sample.

7. After the analyzer finishes aspirating sample, the sample compartment opens. Remove the sample safely
   - The analyzer will automatically run the sample. During this process, the analyzer indicator is flickering in green.
   - When the analysis completes, the analyzer indicator returns to "Ready" status (stay in green).
   - The screen displays the current sample results, histograms, scatter grams and flags (if there is).

Result Reporting

- Reference Range

Parameter	Reference Range
Red Blood Cell Count (RBC)	
	3.5 – 5.8 x 106/mm
Haemoglobin (Hb)	
	10.4 – 14.7 g/dl
Haematocrit (HCT)	
	34.4-48.3 %
MCV	74.3 – 98.3 fl
MCH	25.7– 33.6 pg
MCHC	31.4 – 35.1 g/dl
RDW	11.7 – 15.3 %
White Blood Cell Count (WBC)	3.9 – 10.1 MM3
Differential White Cell Count (Diff)	
Neutrophils	21.4 – 70.5 %

	Lymphocytes		17.8 – 61.8%	
	Monocytes		0 - 13%	
	Eosinophils		0 – 11 %	
	Basophils		0- 2 %	
	Platelet Count		150 – 400 x 10^9/l	
• Panic alert Value	WBC	x10^9/L	<2.0	>50.0
	Hemoglobin	g/dl	<7.0	>22.0
	Hematocrit	%	<20%	>65%
	Platelet	x10^9/L	<30.0	>700.0
Calibration	SC-CAL PLUS Hematology Calibrator Stored in conditions according to product specification (2-8°C).			
Quality Control	• BR60 or BC-60 Hematology Control (H, L, N) or BC-60Hematoloty Control (L,H,N) • BC-RET Hematology Controls			
Test Principle	• WBC Measurement – laser scatter and SF Cube Cell Analysis • RBC/PLT Measurement - Electrical Impedance Method • HGB Measurement - Colorimetric Method			

Annex II Checklist

Code no ----------

MRN----------

Sex----------

Gestational age in week--------

Birth weight in gram----------

Duration of phototherapy in hour----------

Mode of delivery----------

Age at admission

	Before phototherapy	**after phototherapy**
Bilirubin level		
RBC		
Hb		
HTC		
WBC		
Lymphocyte		
Monocyte		
Eosinophil		
Neutrophil		
Basophil		
Platelet count		
PCV		
MCV		
MCH		
MCHC		
RDW		

Annex III Information sheet and Assent Form for Parents/Guardians

Title of the Study: Effect of phototherapy on hematological profile of newborns with unconjugated hyperbilirubinemia at Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia.

Principal Investigator: kidist Ababu (MSc student from Addis Ababa University).

Your permission is being sought to have your child participate in this study. Please read the following information carefully before you decide whether or not to give your permission.

Introduction: You are invited to participate in a research study at Saint Paul's Hospital Millennium Medical College in Addis Ababa, Ethiopia. The study aims to assess the effect of phototherapy on hematological profile of newborns with unconjugated hyperbilirubinemia. Before you decide whether to participate, it is important that you understand the purpose of the study, its procedures, potential risks, and benefits. Please take your time to read this form carefully and feel free to ask any questions.

Purpose of the study: the purpose of this research is to study the effect of phototherapy on hematological profile of newborns with unconjugated hyperbilirubinemia in SPHMMC

Study Description: The study involves monitoring newborns with unconjugated hyperbilirubinemia who will receive phototherapy treatment. We will collect hematological data, such as hemoglobin levels, red blood cell count, white blood cell count, and platelet count, to assess the impact of phototherapy on the hematological profile. Your newborn's blood samples will be collected before and after the phototherapy treatment to measure hematological profile will be carried out in accordance with established medical standards.

Risks and Benefits: The risks associated with this study are minimal and may include discomfort or inconvenience related to blood sampling but experienced sample collectors in NICU uses gentle techniques, ensures a comforting environment, and encourages parental presence to minimize the discomfort.

The benefits include contributing to the understanding of the effect of phototherapy on newborns with unconjugated hyperbilirubinemia, which may improve future neonatal care. but

if the result is clinically significant, we will inform you for further diagnosis and treatment. We will also inform you if your newborn needs further diagnosis and treatment.

Incentives: There is no any payment to be gained by taking part in this research.

Confidentiality: All information and data collected during the study will be kept confidential. No personal information will be disclosed in any research reports or publications.

Voluntary Participation: your assent to allow your child to participate in this study is entirely voluntary. You may choose not to participate or withdraw at any time without any consequences or loss of benefits.

Informed Assent: By signing this form, you acknowledge that you have read and understood the information provided in this document. Your participation in the study is entirely voluntary, and you assent to allow your child to participate. You also understand that the study may involve blood sampling and phototherapy.

Contact persons: If you want to know more information, have any question, you can contact through the researcher and advisor address below.

Principal investigator:

- Kidist Ababu

Tel+251906470975

Advisors:

- Jemal Alemu

Tel+251 911 429989

- Fekadu urgessa

Tel+251 923 330640

- DMLS Ethical review committee +2512755170

You will be provided with a copy of this informed assent form for your records. Thank you for your consideration in participating in this study. Your contribution is greatly appreciated.

Parent/Guardian Assent:

I, _____, the parent/guardian hereby assent to the participation of my child in the research study titled " Effect of phototherapy on hematological profile of newborns with unconjugated hyperbilirubinemia at Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia " The study has been explained to me and my questions answered to my satisfaction and I have received a copy of this informed assent form.

- **Parent/Guardian** Signature: _____**Date:** _____
- **Principal Investigator Signature:**_____ **Date:**_____

Annex IV Amharic version of information sheet and assent form

ለወላጆች/አሳዳጊዎች የመረጃ ወረቀት እና የስምምነት ቅጽ

ስሜ---------- ይባላል። የመጣሁት ክ አዲሰ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ የህክምና ላቦራቶሪ ሳይንስ ትምህርት ቤት ሁለተኛ ዲግሪ ተመራቂ ተማሪ ስሆን በፎቶ ቴራፒ ህክምና በአዲስ የተወለዱ ሕፃናት ሙሉ የደም ህዋስ ምርመራ ላይ የሚያሳድረው ተጽእኖ ለሚሰራዉ ጥናት የመረጃ ሰብሳቢ ነኝ። የዚህ ጥናት ዓላማ በ በቅዱስ ጳውሎስ ሆስፒታል ሚሊኒየም ሜዲካል ኮሌጅ ውስጥ ያልተጣመረ ሃይፐርቢሊሩቢንሚያ ያለባቸው አዲስ የተወለዱ ሕፃናት የፎቶቴራፒ ሕክምና በወሰዱ ሕፃናት ሙሉ የደም ህዋስ ምርመራ ውጤትን ማጥናት ነው። ጥናቱ ያልተቀላቀለ ሃይፐርቢሊሩቢኔሚያ ያለባቸውን የፎቶቴራፒ ህክምና የሚያገኙ አዲስ የተወለዱ ሕፃናትን መከታተልን ያካትታል። የፎቶ ቴራፒ ሙሉ የደም ህዋስ ላይ ያለውን ተጽእኖ ለመገምገም እንደ የሂሞግሎቢን መጠን፣ ቀይ የደም ሴል ብዛት፣ የነጭ የደም ሴል ብዛት እና የፕሌትሌት ብዛት ያሉ የሂማቶሎጂ መረጃዎችን እንሰበስባለን። ሕክምናው እና የመረጃ አሰባሰብ የሚከናወነው በተቀመጡት የሕክምና ደረጃዎች መሠረት ነው.

በቅዱስ ጳውሎስ ሆስፒታል ሚሊኒየም ሜዲካል ኮሌጅ በአዲስ አበባ፣ ኢትዮጵያ በሚደረገው የምርምር ጥናት ላይ እንድትሳተፉ ተጋብዘዋል። ጥናቱ በተወለዱ ሕፃናት ላይ የፎቶ ቴራፒን በ ሙሉ የደም ህዋስ ላይ ተፅእኖ ለመመርመር ያለመ ነው. ለመሳተፍ ከመወሰንዎ በፊት የጥናቱ ዓላማ፣ ሂደቶቹ፣ ሊኖሩ የሚችሉ ስጋቶች እና ጥቅሞቹን መረዳትዎ አስፈላጊ ነው። እባክዎ ይህን ቅጽ በጥንቃቄ ለማንበብ ጊዜዎን ይውሰዱ እና ማንኛውንም ጥያቄ ለመጠየቅ ነፃነት ይሰማዎ።

የጥናት መግለጫ፡ ጥናቱ ያልተቀላቀለ ሃይፐርቢሊሩቢኔሚያ ያለባቸውን የፎቶቴራፒ ህክምና የሚያገኙ አዲስ የተወለዱ ሕፃናትን መከታተልን ያካትታል። የፎቶ ቴራፒ በሙሉ የደም ህዋስ ላይ ያለውን ተጽእኖ ለመገምገም እንደ የሂሞግሎቢን መጠን፣ ቀይ የደም ሴል ብዛት፣ የነጭ የደም ሴል ብዛት እና የፕሌትሌት ብዛት ያሉ የሂማቶሎጂ መረጃዎችን እንሰበስባለን። ሕክምናው እና የመረጃ አሰባሰብ የሚከናወነው በተቀመጡት የሕክምና ደረጃዎች መሠረት ነው.

ስጋቶች እና ጥቅሞች፡ ከዚህ ጥናት ጋር ተያይዘው የሚመጡት አደጋዎች በጣም አናሳ ናቸው እና ከደም ናሙና ጋር በተያያዘ ምቾት ወይም ምቾት ማጣትን ሊያካትቱ ይችላሉ። ሆኖም ግን ናሙናዉ የሚወሰደዉ ልምድ ባላቸዉ ባለሞያ ስለሆነ የህመም ስሜቱ የቀነሰ ነው።

ጥቅሞቹ የፎቶቴራፒ ሕክምና "ያልተጣመረ ሃይፐርቢሊሩቢኔሚያ ባለባቸው አዲስ የተወለዱ ሕፃናት ላይ የሚያስከትለውን በሙሉ የደም ህዋስ ውጤት ለመገንዘብ አስተዋፅዖ ማድረግን ያጠቃልላል ይህም የወደፊት አራስ እንክብካቤን ያሻሽላል።

ማበረታቻዎች፡ በዚህ ጥናት ውስጥ በመሳተፍ ምንም አይነት ክፍያ አያገኙም። ዉጤት ላይ ችግር ካለ በፍጥነት ህክምና ይሰጣችዋል።

ሚስጥራዊነት፡- በጥናቱ ወቅት የሚሰበሰቡ መረጃዎች እና መረጃዎች በሙሉ በሚስጥር ይጠበቃሉ። በማናቸውም የምርምር ዘገባዎች ወይም ህትመቶች ውስጥ ምንም አይነት የግል መረጃ አይገለጽም።

በፈቃደኝነት ተሳትፎ፡ ልጅዎ በዚህ ጥናት እንዲሳተፍ ለመፍቀድ ያለዎት ፈቃድ ሙሉ በሙሉ በፈቃደኝነት ነው። በማንኛውም ጊዜ ላለመሳተፍ ወይም ላለመውጣት መምረጥ ይችላሉ።

በመረጃ የተደገፈ ስምምነት፡ በዚህ ቅጽ ላይ በመፈረም በዚህ ሰነድ ውስጥ የቀረበውን መረጃ እንዳነበቡ እና እንደተረዱት እውቅና ይሰጣሉ። በጥናቱ ውስጥ ያለዎት ተሳትፎ ሙሉ በሙሉ በፈቃደኝነት ነው፣ እና ልጅዎ እንዲሳተፍ ለመፍቀድ ተስማምተዋል።

በዚህ ጥናት ላይ ያለዎትን ጥያቄ በሚከተሉት ኣድራሻ በማንኛውም ጊዜ መጠየቅ ይችላሉ።

የአጥኝው ስም: ቅድስት አባቡ

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የወላጅ/አሳዳጊ ስምምነት፡-

እኔ _____ የ_____

ወላጅ/አሳዳጊ ልጄ በዚህ የምርምር ጥናት ውስጥ እንዲሳተፍ ተስማምቻለሁ "ፎቶ ቴራፒ ህክምና በአዲስ የተወለዱ ሕፃናት ሙሉ የደም ህዋስ ምርመራ ላይ የሚያሳድረው ተጽእኖ" በሚል ርዕስ በተደረገው የምርምር ጥናት ልጄ እንዲሳተፍ ተስማምቻለሁ። ጥናቱ ተብራርቶልኛል እና ለጥያቄዎቼ አጥጋቢ ምላሽ ተሰጥቶኛል እናም የዚህ በመረጃ ላይ የተመሰረተ የስምምነት ቅጽ ቅጂ ተቀብያለሁ።

የወላጅ/አሳዳጊ ፊርማ_____ቀን;-_____

የዋና መርማሪ ፊርማ፡_____ቀን፡- _____

10. Declaration

I, the undersigned, declare that this M.Sc. thesis is my original work, has not been presented for a degree in this or any other university and that all sources of materials used for the thesis have been duly acknowledged.

M.Sc. candidate: **Kidist Ababu**

Signature: _____

Date of submission: _____

This thesis has been submitted with our approval as advisors and co-advisor.

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Signature: _____

Date: _____

Place: Addis Ababa, Ethiopia.

Advisor: Fekadu Urgessa (MSc, PhD candidate)

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