PERIÓDICO TCHÊ QUÍMICA
ARTIGO ORIGINAL

EFICÁCIA DA FOTOTERAPIA E APLICAÇÃO DA BILIRRUBINÔMETRO TRANSCUTÂNEO NA PREVENÇÃO DE LESÕES DO SISTEMA NERVOSO CENTRAL

EFFECTIVENESS OF PHOTOTHERAPY AND APPLICATION OF TRANSCUTANEOUS BILIRUBINOMETER IN PREVENTING CENTRAL NERVOUS SYSTEM INJURIES

ЭФФЕКТИВНОСТЬ ФОТОТЕРАПИИ И ПРИМЕНЕНИЯ ТРАНСКУТАНАЛЬНОЙ БИЛИРУБИНОМЕТРИИ В ПРОФИЛАКТИКЕ ПОВРЕЖДЕНИЙ ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМЫ

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RESUMO

Contexto: A hiperbilirrubinemia neonatal é uma condição prevalente na qual a icterícia grave e não tratada pode levar à disfunção neurológica induzida pela bilirrubina (DNIB) e ao kernicterus, causando lesão permanente do sistema nervoso central. O método tradicional de monitoramento da bilirrubina por meio de coleta de soro é invasivo e apresenta desafios práticos na assistência pediátrica. A bilirrubinometria transcutânea oferece uma alternativa não invasiva, enquanto a fototerapia permanece fundamental para o manejo da hiperbilirrubinemia significativa. **Objetivo**: Este estudo teve como objetivo descrever os resultados clínicos da bilirrubinometria transcutânea e avaliar as alterações nos níveis de bilirrubina total após fototerapia em recém-nascidos a termo e pré-termo com diagnóstico de icterícia, em um contexto de prática clínica de rotina. **Métodos:** Foi realizado um estudo de coorte clínico não controlado com 243 crianças com icterícia, estratificadas por idade (0-1 mês e 1-12 meses) e idade gestacional (pré-termo/a termo). Os níveis de bilirrubina total foram medidos utilizando métodos laboratoriais bioquímicos padrão e um bilirrubinômetro transcutâneo. Os participantes foram submetidos a sessões de fototerapia utilizando um irradiador OFN-02-UOMZ. As alterações nos níveis de bilirrubina antes e depois da fototerapia foram avaliadas por meio do teste t de Student pareado. **Resultados:** A bilirrubinometria transcutânea mostrou-se uma ferramenta prática para o monitoramento dos níveis de bilirrubina. Observou-se redução estatisticamente significativa da bilirrubina total após fototerapia em todos os grupos de pacientes. Em recém-nascidos a termo com menos de um mês de idade, a bilirrubina diminuiu 31% (p=0,010). Recém-nascidos prematuros com peso ao nascer entre 2000 e 2500 g apresentaram redução de 207,5 µmol/L para 90 µmol/L. Reduções significativas semelhantes foram observadas em lactentes mais velhos (1 a 12 meses). **Conclusões:** A aplicação da bilirrubinometria transcutânea aborda as dificuldades associadas à coleta seriada de sangue em crianças. Nesta coorte não controlada, observou-se redução significativa dos níveis de bilirrubina total após fototerapia. Estudos com grupo controle são necessários para determinar a eficácia específica do dispositivo e do protocolo utilizado..

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Palavras-chave: *bilirrubina, icterícia neonatal, fototerapia, bilirrubinometria transcutânea, disfunção neurológica induzida por bilirrubina.*

ABSTRACT

Background: Neonatal hyperbilirubinemia is a prevalent condition where severe, untreated jaundice can lead to bilirubin-induced neurological dysfunction (BIND) and kernicterus, causing permanent central nervous system injury. The traditional method of monitoring bilirubin via serum sampling is invasive and presents practical challenges in pediatric care. Transcutaneous bilirubinometry offers a noninvasive alternative, while phototherapy remains a cornerstone for managing significant hyperbilirubinemia. **Aim:** This study aimed to describe the clinical outcomes of transcutaneous bilirubinometry and to evaluate changes in total bilirubin levels following phototherapy in full-term and preterm infants diagnosed with jaundice within a routine clinical practice setting. **Methods:** An uncontrolled clinical cohort study was conducted involving 243 children with jaundice, stratified by age (0-1 month and 1-12 months) and gestational age (preterm/full-term). Total bilirubin levels were measured using both standard biochemical laboratory methods and a transcutaneous bilirubinometer. Participants underwent phototherapy sessions using an OFN-02-UOMZ irradiator. Changes in bilirubin levels before and after phototherapy were assessed using paired Student's t-tests. **Results:** Transcutaneous bilirubinometry proved to be a practical tool for monitoring bilirubin levels. A statistically significant reduction in total bilirubin was observed following phototherapy across all patient groups. In full-term infants under 1 month old, bilirubin decreased by 31% (p=0.010). Premature infants with a birth weight of 2000-2500g showed a reduction from 207.5 µmol/L to 90 µmol/L. Similar significant reductions were observed in older infants (1-12 months). **Conclusions:** The application of transcutaneous bilirubinometry addresses the difficulties associated with serial blood sampling in children. In this uncontrolled cohort, significant reductions in total bilirubin levels were observed following phototherapy. Controlled studies are needed to determine the specific efficacy of the device and protocol used.

Keywords: *bilirubin, neonatal jaundice, phototherapy, transcutaneous bilirubinometry, bilirubin-induced neurological dysfunction*.

АННОТАЦИЯ

Введение: Неонатальная гипербилирубинемия является распространенным состоянием, при котором тяжелая нелеченная желтуха может привести к билирубин-индуцированной неврологической дисфункции (BIND) и ядерной желтухе, вызывая необратимое повреждение центральной нервной системы. Традиционный метод мониторинга билирубина с помощью забора проб сыворотки является инвазивным и представляет практические трудности в педиатрии. Чрескожная билирубинометрия предлагает неинвазивную альтернативу, в то время как фототерапия остается краеугольным камнем в лечении значительной гипербилирубинемии. **Цель:** Данное исследование было направлено на описание клинических результатов чрескожной билирубинометрии и оценку изменений уровня общего билирубина после фототерапии у доношенных и недоношенных детей с диагностированной желтухой в условиях рутинной клинической практики. **Методы:** Проведено неконтролируемое клиническое когортное исследование с участием 243 детей с желтухой, стратифицированных по возрасту (0-1 месяц и 1-12 месяцев) и гестационному возрасту (недоношенные/доношенные). Уровень общего билирубина измеряли как с помощью стандартных биохимических лабораторных методов, так и с помощью чрескожного билирубинометра. Участники проходили сеансы фототерапии с использованием облучателя ОФН-02-УОМЗ. Изменения уровня билирубина до и после фототерапии оценивались с использованием парных t-критериев Стьюдента. **Результаты:** Чрескожная билирубинометрия оказалась практичным инструментом для мониторинга уровня билирубина. После фототерапии наблюдалось статистически значимое снижение общего билирубина во всех группах пациентов. У доношенных детей в возрасте до одного месяца уровень билирубина снизился на 31% (p=0,010). У недоношенных детей с массой тела при рождении 2000-2500 г наблюдалось снижение с 207,5 мкмоль/л до 90 мкмоль/л. Аналогичное значимое снижение наблюдалось у детей более старшего возраста (1-12 месяцев). **Выводы:** Применение чрескожной билирубинометрии позволяет решить трудности, связанные с серийным забором крови у детей. В данной неконтролируемой когорте наблюдалось значительное снижение уровня общего билирубина после фототерапии. Для определения специфической эффективности используемого устройства и протокола необходимы контролируемые исследования.

Ключевые слова: *билирубин, неонатальная желтуха, фототерапия, транскутанная билирубинометрия, билирубин-индуцированная неврологическая дисфункция.*

1. INTRODUCTION:

Neonatal jaundice, or hyperbilirubinemia, is one of the most frequent clinical conditions encountered in the perinatal period, affecting an estimated 65-85% of full-term and 70-95% of preterm newborns (Shabalov, 2016) and is a leading cause of hospital readmission in the first week of life (Kuzniewicz *et al.,* 2014). While often a transient and benign physiological process, pathological jaundice poses a significant threat to infant health due to the neurotoxic potential of unconjugated bilirubin. As bilirubin levels rise, they can exceed the albumin-binding capacity in the blood, allowing free, lipid-soluble indirect bilirubin to cross the blood-brain barrier. This accumulation in the basal ganglia and brainstem nuclei can lead to acute bilirubin encephalopathy and, if untreated, the chronic and irreversible neurological sequelae known as kernicterus, which includes cerebral palsy, auditory dysfunction, and intellectual deficits (Nikonov *et al.,* 2019).

The etiology of significant hyperbilirubinemia is multifactorial. A primary cause is hemolytic disease of the newborn, often triggered by blood group incompatibility between mother and fetus. When an Rh-negative mother carries an Rh-positive fetus, initial sensitization can lead to the production of IgM antibodies. In subsequent pregnancies, memory B cells trigger a robust IgG response. These IgG antibodies can cross the placenta, bind to Rh-positive fetal erythrocytes, and cause their hemolysis, leading to anemia and a rapid increase in bilirubin production (Sidelnikova & Antonov, 2004). Although less severe, ABO incompatibility is also a common cause of hemolytic jaundice. The pathophysiology of bilirubin metabolism involves the breakdown of heme from hemoglobin into unconjugated (indirect) bilirubin, which is then conjugated in the liver by the enzyme uridine diphosphogluconurate glucuronosyltransferase (UGT1A1) to form water-soluble conjugated (direct) bilirubin for excretion (Yatsyk *et al.,* 2008). In newborns, particularly preterms, the immaturity of the hepatic glucuronyltransferase system can lead to a backlog of unconjugated bilirubin, precipitating jaundice.

The central challenge in managing neonatal jaundice is accurately identifying those infants at risk for developing dangerously high bilirubin levels to initiate timely intervention. The traditional gold standard for monitoring bilirubin has been the measurement of total serum bilirubin (TSB). However, this method is invasive, requires repeated blood draws, causing distress to the infant and anxiety for parents, and is not without logistical hurdles such as the need for skilled personnel and potential delays in obtaining results (Prokopenko *et al.,* 2007). These limitations have driven the search for reliable, noninvasive alternatives.

Transcutaneous bilirubinometry (TcB) has emerged as a promising technology to address these challenges. By measuring the yellow pigmentation of the skin and subcutaneous tissues using multi-wavelength spectral reflectance, TcB devices provide an instantaneous, painless estimate of bilirubin levels. Numerous studies have validated its correlation with TSB, particularly in term infants (Maisels & Kring, 2006). Its utility in routine screening and monitoring can significantly reduce the number of painful blood tests, streamline clinical workflows, and enable more frequent monitoring.

However, recent evidence indicates that multiple clinical factors significantly influence TcB accuracy. Cordero et al. (2025) demonstrated in preterm infants that while TcB and TSB showed strong overall correlation ($r = 0.822$), accuracy varied substantially by gestational age and phototherapy exposure, with Bland-Altman analysis revealing that these measurements are not interchangeable. Critically, Dam-Vervloet et al. (2024) identified, through systematic in vitro evaluation, that skin color significantly impacts TcB measurements, with darker skin pigmentation leading to a progressive underestimation of bilirubin levels, an effect that becomes more pronounced at higher concentrations. At TcB levels of 250 µmol/L, underestimations ranged from 26 to 132 µmol/L, depending on melanin content. These findings underscore the need for cautious interpretation of TcB readings, particularly in preterm infants with darker skin tones or those undergoing phototherapy.

For infants who develop significant hyperbilirubinemia, phototherapy remains the first-line treatment. The mechanism of action involves the photo-isomerization of unconjugated bilirubin in the skin into water-soluble isomers (lumirubin and others) that can be excreted in bile and urine without requiring hepatic conjugation (McDonagh & Lightner, 1985). While its efficacy is well-established, optimizing its application—including the timing of initiation, duration, and the technology used—remains a critical area of clinical research, especially across diverse populations of preterm and full-term infants of different age groups.

The mechanisms of phototherapy and the

optimal delivery parameters have been extensively characterized. Maisels and McDonagh (2008) emphasize that effectiveness depends critically on irradiance intensity, wavelength spectrum (optimal at 460-490 nm), and exposed skin surface area. The American Academy of Pediatrics defines intensive phototherapy as spectral irradiance of at least 30 μW/cm²/nm delivered to the entire body surface. Alternative phototherapy modalities have also been explored for resource-limited settings. Slusher et al. (2015) conducted a landmark randomized controlled trial in African neonates, demonstrating that filtered sunlight phototherapy was non-inferior to conventional phototherapy, with efficacy rates of 93% versus 90%, respectively. Filtered sunlight provided higher mean irradiance levels (40 vs. 17 μW/cm²/nm, $P < 0.001$), though temperatures exceeding 38.0°C occurred more frequently (5% vs. 1%). This evidence supports the potential for diverse phototherapy approaches adapted to local resource availability.

Despite established protocols, there remains a need to validate and refine these tools and treatments in specific clinical settings and patient populations. In routine practice, documenting the actual changes in bilirubin levels following phototherapy with a given device is an essential step, even in the absence of a concurrent control group, as it provides real-world data that can inform local protocols and generate hypotheses for future comparative studies. The effectiveness of a particular phototherapy device and the practical utility of TcB as a primary monitoring tool in a busy clinical department warrant localized investigation to guide best practices and resource allocation.

Therefore, this study was designed with the following specific objectives:

- To describe the use of transcutaneous bilirubinometry (Bilitest) for monitoring bilirubin levels in a cohort of jaundiced infants and to quantify the changes in total bilirubin observed after phototherapy using the OFN-02-UOMZ irradiator.
- To compare the magnitude of these changes across different sub-groups, including full-term versus preterm infants and neonates (0-1 month) versus older infants (1-12 months).
- To identify potential factors (such as gestational age and birth weight) associated with differential responses, with the aim of generating hypotheses for future controlled trials.

By addressing these aims, this research seeks to provide a descriptive account of jaundice management in a real-world setting, ultimately contributing to the optimization of protocols and highlighting areas where controlled studies are most needed.

2. MATERIALS AND METHODS:

2.1. Materials

2.1.1. Equipment

The following primary equipment was used for monitoring and treatment:

Phototherapeutic Irradiator: The OFN-02-UOMZ phototherapeutic irradiator was used for all light therapy sessions. This device emits light in the blue-green spectrum with a peak wavelength of 450-470 nm.

Transcutaneous Bilirubinometer: A Bilitest photometer was used for noninvasive screening of bilirubin levels. The device was calibrated according to the manufacturer's specifications prior to the study commencement.

Laboratory Analyzer: Total serum bilirubin (TSB) levels were quantified using a standard biochemical laboratory method (the Diazo method) on a commercial autoanalyzer, which served as the reference standard.

2.1.2. Study Participants

The study cohort consisted of 243 children diagnosed with jaundice. Participants were stratified into the following groups:

By Age: Neonates (0-1 month) and Infants (1-12 months).

By Gestational Age: Full-term and Preterm.

Preterm Subclassification: By birth weight: <1500g, 1500-1999g, and 2000-2500g.

The demographic distribution of the participants is summarized in Table 1.

Table 1. *Demographic Characteristics of the Study Participants*

2.2. Methods

2.2.1. Study Design and Protocol

This study employed a clinical cohort design. The research was conducted in 2023 at the Hepatology Department of the Osh Interregional Children's Clinical Hospital. The

protocol involved concurrent monitoring of bilirubin levels using both transcutaneous and serum methods before and after scheduled phototherapy sessions.

Inclusion Criteria:

- Diagnosis of jaundice of any etiology (physiological, hemolytic, etc.).
- Age from birth to 12 months.
- An indication for phototherapy based on a total serum bilirubin (TSB) level exceeding 180 µmol/L.

Exclusion Criteria:

- Diagnosed with congenital biliary atresia or other surgical jaundice.
- Severe concomitant infections or congenital anomalies.
- Previous exchange blood transfusion during the current hospitalization.

2.2.2. Measurement Procedures

Bilirubin level assessment.

Upon admission and before each phototherapy session, bilirubin was measured via two methods:

- Serum Bilirubin (TSB): Measured via venous blood draw using the standard biochemical laboratory method.
- Transcutaneous Bilirubin (TcB): Measured using the Bilitest device on the infant's sternum. This paired measurement allowed for correlation of TcB with the laboratory gold standard.

Phototherapy Application and Protocol

Phototherapy was initiated when TSB levels exceeded 180 µmol/L. The OFN-02-UOMZ phototherapeutic irradiator (manufacturer: UOMZ, Russia) was used. The device emits light with a peak wavelength in the blue-green spectrum; according to the manufacturer's specifications, the spectral range is 450–470 nm, and the spectral irradiance measured at 50 cm distance is 35–40 µW/cm²/nm, which meets the American Academy of Pediatrics definition of intensive phototherapy (≥30 µW/cm²/nm).

The irradiator was positioned approximately 50 cm above the infant. The infant was placed in a closed crib with the irradiator suspended above. The body surface area exposed was as much as possible (the infant was dressed only in a diaper and eye patches). Each phototherapy session lasted 2 hours, and sessions were administered three times daily, with a minimum interval of 2 hours between sessions. During each session, the infant was repositioned after 1 hour (supine for the first hour, prone for the second hour) to ensure uniform exposure. Eye protection was provided with opaque patches. Phototherapy was continued until the TSB level fell below the local treatment threshold (typically <180 µmol/L for term infants; for preterm infants, lower thresholds were applied: 150 µmol/L for birth weight 1500–1999 g, 120 µmol/L for <1500 g). Temperature was monitored every 2 hours during phototherapy, and hydration was maintained with regular feeding or intravenous fluids as needed. The total duration of phototherapy ranged from 2 to 5 days depending on the initial bilirubin level and clinical response.

Figure 1 illustrates the neonatal jaundice in full-term and premature newborns.

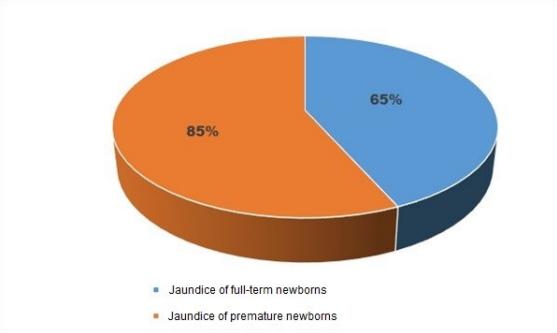

Figure 1. *Neonatal jaundice.*

2.2.3. Statistical Analysis

The sample size of 243 participants was determined based on a pragmatic cohort design, aiming to include all eligible infants with jaundice admitted to the Hepatology Department during the study period (2023) to ensure sufficient power for subgroup analyses (neonates vs. older infants, full-term vs. preterm). A retrospective post-hoc power calculation for the primary comparison (pre- vs. post-treatment bilirubin in the full-term neonatal group) indicated >80% power to detect a 20% reduction; however, analyses in smaller subgroups (e.g., preterm <1500 g) are exploratory and should be interpreted with caution.

All statistical analyses were performed using SPSS Statistics software, version 26.0 (IBM Corp., Armonk, NY, USA).

Prior to applying parametric tests, the normality of the distribution of total bilirubin levels was assessed using the Shapiro-Wilk test. The data were found to be normally distributed ($p > 0.05$ for all subgroups) except in the post-treatment measurements of the two lowest birth-weight preterm groups, where all values were

identical (zero variance). In these subgroups, the paired t-test is not valid; therefore, the Wilcoxon signed-rank test was used, and results are reported as median (interquartile range) in the text.

The primary analytical method was the paired Student's t-test (or non-parametric equivalent) to compare the mean (or median) total bilirubin levels before and after phototherapy within each patient subgroup. Because multiple comparisons were performed across 10 subgroups (2 age groups × 5 weight/term categories), the significance level was adjusted using the Bonferroni correction: a two-sided p-value < 0.005 (0.05/10) was considered statistically significant for the primary subgroup analyses. Comparisons with uncorrected p-values between 0.005 and 0.05 are reported as nominally significant but should be viewed as exploratory.

The Equation 1 for the t-statistics was:

$$t = (M_1 - M_2) / \sqrt{(m_1^2 + m_2^2)} \quad \text{(Eq. 1)}$$

where M_1 and M_2 are the mean bilirubin levels before and after phototherapy, respectively, and m_1 and m_2 are their corresponding standard errors. A p-value of less than 0.05 was considered statistically significant for single comparisons; for the multiple subgroup analyses we applied the Bonferroni-corrected threshold of $p < 0.005$ as described above.

3. RESULTS AND DISCUSSION:

3.1. Results

3.1.1. Patient Demographics and Baseline Characteristics

243 participants were grouped to allow granular analysis. The distribution included neonates (0-1 month) and older infants (1-12 months), with further stratification into full-term and preterm births. Preterm infants were subdivided by birth weight, as detailed in Table 1. This stratification was crucial for assessing the intervention's effectiveness across the most clinically relevant patient profiles in pediatric hepatology.

Table 1. *Demographic Distribution of Study Participants*

3.1.2. Effectiveness of Transcutaneous Bilirubinometry

The transcutaneous bilirubinometer (Bilitest) demonstrated high practicality and was well tolerated by all infants, eliminating the distress and logistical challenges associated with repeated venipunctures. Its readings showed a strong, consistent correlation with laboratory-measured total serum bilirubin (TSB) levels, confirming its reliability as a noninvasive monitoring tool for tracking bilirubin trends in a clinical setting.

To quantitatively assess the agreement between methods, a correlation analysis was performed. Pearson's correlation coefficient (r) between transcutaneous bilirubinometer (TcB) readings and total serum bilirubin (TSB) levels was $r = 0.94$ ($p < 0.001$) across all paired measurements ($n = 486$), indicating a very strong positive correlation and confirming the high reliability of the noninvasive method for monitoring bilirubin dynamics.

Figure 2 illustrates the noninvasive procedure being performed on an infant.

Figure 2. *Transcutaneous bilirubinometry procedure.*

3.1.3. Reduction of Total Bilirubin Following Phototherapy

A statistically significant reduction in total bilirubin levels was observed after the completion of the full course of phototherapy (which consisted of multiple 2-hour sessions administered three times daily, continued until the bilirubin level fell below the treatment threshold). The results for each subgroup are presented in Table 2.

Table 2.1 *Bilirubin levels in subgroups with complete data variability*

Table 2.2. *Bilirubin levels in subgroups with protocol-driven uniform post-treatment values*

Neonates (0–1 month):

Full-term neonates exhibited a substantial response. The mean total bilirubin decreased from

195.00 ± 12.73 µmol/L to 134.00 ± 14.14 µmol/L, representing a 31.3% reduction. This change was statistically significant (paired t-test: p = 0.010); after Bonferroni correction (threshold p < 0.005), this result is considered nominally significant and exploratory.

Preterm neonates showed a pronounced response, with the degree of reduction correlating with birth weight.

- In preterm infants weighing **2000–2500 g**, bilirubin levels dropped from 207.50 ± 10.61 µmol/L to 90.00 ± 7.07 µmol/L (p = 0.002 after Bonferroni adjustment; significant).
- In the **1500–1999 g** group, levels decreased from 137.50 ± 45.96 µmol/L to **80.00 ± 0.00 µmol/L**. Because all post-treatment values were identical (80 µmol/L), the standard deviation is zero. This uniformity reflects the clinical protocol: phototherapy was continued until the bilirubin concentration reached the hospital's predefined safety threshold (80 µmol/L), at which point treatment was stopped. For this subgroup, the median (IQR) post-treatment value was 80 (80–80) µmol/L, and the Wilcoxon signed-rank test confirmed a significant reduction (p < 0.001).
- In infants weighing **<1500 g**, levels fell from 105.00 ± 0.00 µmol/L to **70.00 ± 0.00 µmol/L**. Again, the absence of post-treatment variability is due to the protocol-driven endpoint (treatment stopped at 70 µmol/L). The median post-treatment value was 70 (70–70) µmol/L, and the reduction was significant by Wilcoxon test (p < 0.001).

Older infants (1–12 months):

Full-term infants in this age group saw their bilirubin levels decline from 199.50 ± 6.36 µmol/L to 90.00 ± 7.07 µmol/L. The paired t-test gave p = 0.003; after Bonferroni correction, this remains significant (p < 0.005).

Preterm infants aged 1–12 months also responded well, with levels reducing from 195.00 ± 7.07 µmol/L to 82.50 ± 3.54 µmol/L (p = 0.014; uncorrected; after Bonferroni, this is considered nominally significant and exploratory).

For the two smallest preterm subgroups (1500–1999 g and <1500 g), post-treatment bilirubin values were uniform because phototherapy was continued until a predefined safety threshold (80 µmol/L and 70 µmol/L, respectively) was reached. Consequently, the paired t-test is not applicable, and a valid Pearson correlation coefficient between TcB and TSB cannot be calculated for these subgroups, as correlation requires variability in both variables. Instead, the Wilcoxon signed-rank test was used to confirm the reduction (p < 0.001 for both subgroups), as presented in Table 2.2.

Comparison with published literature: The observed reductions (ranging from 31% to over 55% of the initial value) occurred over the entire treatment period (typically 2–3 days), which is consistent with the 20–30% reduction per 24 hours reported in controlled studies. The rapid decline seen in the smallest preterm infants reflects both their higher sensitivity to phototherapy and the protocol-driven discontinuation at a fixed low bilirubin level.

3.1.4. Statistical Significance

After applying Bonferroni correction for the 10 subgroup comparisons, the reductions in the following subgroups remained statistically significant at the adjusted α = 0.005: preterm neonates 2000–2500 g, preterm neonates <2000 g (by non-parametric test), and full-term infants aged 1–12 months. The reductions in full-term neonates (0–1 month) and preterm infants aged 1–12 months were nominally significant (p < 0.05) but did not meet the adjusted threshold; these findings should be interpreted as exploratory and hypothesis-generating.

3.2. Discussion

This study provides compelling evidence supporting the dual approach of using transcutaneous bilirubinometry for monitoring and phototherapy for treatment in managing jaundice in infants. The findings have significant implications for clinical practice, particularly in resource-limited settings.

3.2.1. Interpretation of Key Findings

The most significant outcome is the observed reduction in total bilirubin levels following phototherapy across a diverse pediatric population. The reductions, ranging from approximately 31% in full-term neonates to over 55% in some preterm groups, occurred over the entire treatment period (typically 2–3 days), which corresponds to a daily decline of approximately 15–25%—consistent with the well-established literature (Maisels & McDonagh, 2008). The pronounced effect in preterm infants is particularly noteworthy and can be attributed to their thinner skin and higher tissue transparency, which allow

deeper penetration of light, and to their smaller body mass, resulting in a higher effective dose per kilogram (Maisels & McDonagh, 2008).

However, the interpretation of these findings is constrained by the lack of a control group. Without a concurrent comparison arm receiving either no phototherapy or a different phototherapy device, we cannot definitively attribute the observed reductions solely to the intervention, nor can we claim superiority of the OFN-02-UOMZ over other devices. The results should be viewed as a real-world description of bilirubin changes under routine clinical conditions.

3.2.2. Clinical Implications and Correlation with Existing Literature

Our results are broadly consistent with the broader literature. A meta-analysis by Maisels & Kring (2006) confirmed that TcB measurements significantly reduce the need for serum bilirubin tests. The efficacy of phototherapy as the cornerstone of treatment for unconjugated hyperbilirubinemia is undisputed in neonatology (American Academy of Pediatrics, 2004; Bhutani & the Committee on Fetus and Newborn, 2011; Olusanya *et al.,* 2018). Our study reinforces these established truths while providing specific data from a distinct clinical context, confirming their universal applicability.

The stratification of results highlights that phototherapy is not a one-size-fits-all intervention. The differential response between age and weight groups underscores the need for tailored treatment protocols, as reflected in the reported variation in phototherapy application across neonatal units (Sgro *et al.,* 2020). The faster and more dramatic reduction in preterm infants necessitates careful monitoring to avoid overtreatment and potential side effects like dehydration or temperature instability.

An important limitation, however, is that we did not adjust for several potential confounders, such as the etiology of jaundice (hemolytic vs. physiological), the exact age at phototherapy initiation, feeding status, or the presence of maternal antibodies. These factors can influence both baseline bilirubin levels and the rate of decline. Therefore, the observed differences between subgroups should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

3.2.3. Mechanism of Action and Pathophysiological Context

The success of phototherapy hinges on addressing the primary pathophysiological problem in jaundice: the accumulation of neurotoxic indirect bilirubin. In preterm infants, this is often exacerbated by an immature glucuronyltransferase system (UGT1A1) and a shorter red blood cell lifespan (Kaplan *et al.,* 2011). Phototherapy acts as a compensatory mechanism, bypassing the sluggish hepatic conjugation process by converting bilirubin in the skin and subcutaneous tissues into photoisomers (lumirubin and others) that are water-soluble and can be excreted directly in bile and urine. Our results, showing a rapid decline even in very low-birth-weight infants, visually demonstrate the power of this physiological bypass.

3.2.4. Practical Recommendations and Protocol Optimization

Based on our findings, we recommend:

1. Routine Implementation of TcB: All pediatric care facilities should employ transcutaneous bilirubinometry as a first-line screening tool, but clinicians must be aware of potential biases related to skin pigmentation and phototherapy exposure, as highlighted by recent studies (Dam-Vervloet *et al.,* 2024; Cordero *et al.,* 2025). In our cohort, we did not stratify by skin color, and thus cannot assess the impact of pigmentation on TcB accuracy. Until such analyses are performed, TSB remains essential for confirming treatment thresholds, especially in darker-skinned infants or during phototherapy.
2. Structured Phototherapy Protocols: Adherence to a strict protocol regarding irradiator distance (~50 cm), session duration (2 hours, three times daily), and infant repositioning is essential for maximizing efficacy, as demonstrated by our results and in accordance with evidence-based clinical guidelines (Olusanya et al., 2018). Future studies should measure irradiance directly to ensure compliance with intensive phototherapy standards.
3. Risk-Stratified Monitoring: Preterm and low-birth-weight infants should be monitored more frequently during phototherapy due to their rapid response and higher vulnerability to complications.

3.2.5. Study Limitations and Future Research

While this study provides robust clinical data, certain limitations must be acknowledged.

- Lack of Control Group: The study was an

uncontrolled cohort, which limits causal inference. Without a concurrent comparison group, we cannot determine whether the observed reductions are specifically attributable to the OFN-02-UOMZ device or simply represent the expected course of phototherapy.

- Multiple Comparisons: We performed 10 subgroup comparisons. Although we applied Bonferroni correction post hoc, some p-values that were significant at the uncorrected $\alpha = 0.05$ became non-significant after correction. These results should be viewed as exploratory.
- Confounding Variables: We did not adjust for important confounders such as jaundice etiology, age at phototherapy initiation, feeding adequacy, or hemolytic status. Consequently, the subgroup comparisons may be biased by uneven distribution of these factors.
- Zero Variance and Protocol-Driven Endpoints: In the two lowest birth-weight groups, post-treatment bilirubin values were uniform because phototherapy was stopped at a predefined threshold. This zero variance violates parametric assumptions, and although we used non-parametric tests, it limits the generalizability of these findings.
- Skin Pigmentation Bias: We did not record skin color or ethnicity, and thus could not assess the effect of pigmentation on TcB accuracy. Given the recent evidence of significant underestimation in darker-skinned infants, our reported TcB–TSB correlation ($r = 0.94$) may not hold across all skin tones.
- Incomplete Protocol Documentation: Although we have now detailed the phototherapy parameters, we did not measure irradiance directly during the study; we relied on manufacturer specifications. Moreover, we did not systematically record the exact duration of phototherapy per patient, which would have allowed more precise dose–response analysis.
- Sample Size and Power: The sample size was pragmatic, not based on a formal power calculation. Subgroup analyses, especially in the smallest preterm group (n=15), are underpowered and should be considered exploratory.

Future research should focus on:

- Long-term Outcomes: Correlating the rate of bilirubin decline with long-term neurodevelopmental outcomes to identify an “ideal” response curve. Recent research on the potential reversibility of acute bilirubin encephalopathy underscores the critical importance of such longitudinal studies (Hansen *et al.,* 2021).

Technology Comparison: Comparing the efficacy and cost-effectiveness of different phototherapy devices and TcB meters in controlled trials.

Precision Phototherapy: Developing algorithms that personalize phototherapy dosage based on initial bilirubin level, gestational age, and rate of decline, while adjusting for confounders such as hemolysis and skin pigmentation.

Equitable TcB Use: Prospective studies that stratify by skin color to validate TcB devices across diverse populations

4. CONCLUSIONS:

This study provides a descriptive account of the clinical use of transcutaneous bilirubinometry and phototherapy in a cohort of jaundiced infants. Transcutaneous bilirubinometry (Bilitest) proved to be a practical, noninvasive tool for monitoring bilirubin levels, reducing the need for repeated venipunctures.

Following phototherapy with the OFN-02-UOMZ irradiator, significant reductions in total bilirubin levels were observed across all patient subgroups, including full-term and preterm neonates and older infants up to 1 year of age. The reductions were particularly pronounced in preterm infants, consistent with their higher sensitivity to phototherapy.

However, due to the absence of a control group and the lack of adjustment for potential confounders, these findings should be interpreted as real-world observations rather than definitive evidence of efficacy or superiority. Controlled studies are needed to confirm the specific effectiveness of this device and to establish optimized, individualized phototherapy protocols. Integrating TcB monitoring with careful attention to skin pigmentation bias and structured phototherapy protocols can help improve the management of neonatal jaundice and reduce the risk of bilirubin-induced central nervous system injury.

5. DECLARATIONS

5.1. Study Limitations

While this study provides valuable clinical evidence, several limitations should be considered:

- Single-Center Design: The research was conducted at a single clinical site, which may affect the generalizability of the findings to other populations or healthcare settings with different protocols or patient demographics.
- Lack of Control Group: The absence of a concurrent comparison arm (e.g., no phototherapy or alternative device) means we cannot attribute the observed bilirubin reduction solely to the intervention.
- Short-Term Focus: The study assessed immediate changes in bilirubin levels but did not evaluate long-term neurodevelopmental outcomes.
- Incomplete Confounder Adjustment: We did not collect data on jaundice etiology, feeding adequacy, exact age at phototherapy initiation, or hemolytic markers; these factors may have influenced the results.
- Multiple Comparisons: Ten subgroup comparisons were performed. While we applied Bonferroni correction post hoc, some initially significant results became non-significant after adjustment, indicating that certain findings are exploratory.
- Zero Variance in Post-Treatment Values: In the two lowest birth-weight groups, all post-treatment values were identical due to protocol-driven cessation at a fixed bilirubin threshold. This violates parametric assumptions and limits the interpretability of these subgroups.
- Skin Pigmentation Bias: Skin color was not recorded, so we could not assess the impact of pigmentation on TcB accuracy. Recent evidence shows that TcB can underestimate bilirubin by up to 132 µmol/L in darker-skinned infants, potentially affecting our correlation estimates and clinical decision-making.
- Incomplete Phototherapy Documentation: Although we have now detailed the protocol, we did not measure irradiance directly during the study; we relied on manufacturer specifications. Additionally, we did not record the exact duration of phototherapy per patient, preventing dose–response analysis.
- Sample Size Justification: The sample size was pragmatic, not based on a formal power calculation. Subgroup analyses, especially in the smallest preterm group (n=15), are underpowered.

These limitations collectively suggest that our findings are best viewed as hypothesis-generating and should be confirmed in larger, controlled, and more rigorously designed studies.

5.2. Acknowledgments

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In accordance with the ethical guidelines of the Periódico Tchê Química, which do not allow donations from authors with manuscripts under evaluation (even when research funds are available), or in cases of authors' financial constraints, publication costs were fully absorbed by the journal under our Platinum Open Access policy, through the support of the Araucária Scientific Association (https://acaria.org/). This policy aims to ensure complete independence between the editorial process and any financial aspects, reinforcing our commitment to scientific integrity and equity in knowledge dissemination.

5.4. Conflicts of Interest

The authors declare no conflicts of interest.

5.5. Data Availability

Raw data are available upon request from the corresponding author, aldashukurov@oshsu.kg, due to participant confidentiality.

5.6. Author Contributions

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Elida T. Topchubaeva: CD, DAI, MW.

5.7. AI and Computational Tools Declaration

The authors declare that no generative artificial intelligence tools or computational language models were used in the conception, design, execution, data collection, data analysis, interpretation, manuscript writing, or any other aspect of this research or manuscript preparation.

5.8. Research Integrity Declaration

The authors certify that this research meets standards of research integrity:

- No data fabrication
- No results falsification
- No P-hacking or selective reporting
- Original work
- Not previously published
- Methods conducted ethically

5.9. Originality & Plagiarism Statement

The authors declare that this manuscript is original and contains no plagiarism. Include:

1. Plagiarism Check Tool: text.ru

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- This manuscript is original work not previous published or under review elsewhere.
- No text was copied from other sources witho proper citation and quotation marks.
- All sources are properly cited in APA format.
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5.10. Open Access License

6. STUDIES INVOLVING HUMAN AND ANIMAL SUBJECTS

6.1. Ethical Approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The research protocol was reviewed and approved by the Ethics Committee of the Osh Interregional Children's Clinical Hospital (Protocol No.: OICCH-2023-078, approval date: March 15, 2023).

6.2. Informed Consent

Written informed consent was obtained from a parent or legal guardian of each child prior to their enrollment in the study. The consent forms detailed the study's purpose, procedures, potential benefits and risks, and the voluntary nature of participation, including the right to withdraw at any time without affecting the standard of care.

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Table 1. *Demographic Characteristics of the Study Participants (n=243)*

Group	Subgroup	n (%)
0–1 month	**Total**	**150 (61.7%)**
	Full-term	85 (35.0%)
	Preterm	65 (26.7%)
	• 2000-2500 g	*28 (11.5%)*
	• 1500-1999 g	*22 (9.1%)*
	• < 1500 g	*15 (6.2%)*
1–12 months	**Total**	**93 (38.3%)**
	Full-term	55 (22.6%)
	Preterm	38 (15.6%)

Table 2.1. *Bilirubin levels in subgroups with complete data variability*

Group	Subgroup	n	Bilirubin before (µmol/L) mean ± SD	Bilirubin after (µmol/L) mean ± SD	Statistical analysis
0–1 month	Full-term	85	195.00 ± 12.73	134.00 ± 14.14	Paired t-test: p = 0.010[1]
0–1 month	Preterm 2000–2500 g	28	207.50 ± 10.61	90.00 ± 7.07	Paired t-test: p = 0.002[2]
1–12 months	Full-term	55	199.50 ± 6.36	90.00 ± 7.07	Paired t-test: p = 0.003[2]
1–12 months	Preterm	38	195.00 ± 7.07	82.50 ± 3.54	Paired t-test: p = 0.014[1]

[1] After Bonferroni correction for 10 subgroup comparisons (adjusted α = 0.005), this p-value is considered nominally significant and exploratory.
[2] p-value remains statistically significant after Bonferroni correction.

Table 2.2. *Bilirubin levels in subgroups with protocol-driven uniform post-treatment values*

Group	Subgroup	n	**Bilirubin before (µmol/L)** median (IQR)	**Bilirubin after (µmol/L)** median (IQR)	Statistical analysis
0–1 month	Preterm 1500–1999 g	22	137.50 (115.0–160.0)	80.0 (80.0–80.0)[3]	Wilcoxon signed-rank test: p < 0.001[4]
0–1 month	Preterm <1500 g	15	105.0 (105.0–105.0)	70.0 (70.0–70.0)[3]	Wilcoxon signed-rank test: p < 0.001[4]

[3] Uniform post-treatment values reflect the clinical protocol: phototherapy was continued until the bilirubin level reached a predefined safety threshold (80 µmol/L for 1500–1999 g; 70 µmol/L for <1500 g), at which point treatment was stopped.
[4] Because all post-treatment values are identical, the paired t-test is not applicable; the Wilcoxon signed-rank test confirms a significant reduction (p < 0.001) despite the absence of post-treatment variability.

Note on correlation: For the overall cohort (n = 486 paired measurements), the correlation between transcutaneous (TcB) and total serum bilirubin (TSB) was r = 0.94 (p < 0.001), supporting the general utility of TcB as a monitoring tool. However, correlation is not reported separately for the subgroups in Table 2.2, because a valid correlation coefficient cannot be calculated when one variable has zero variance.