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RESEARCH

Continuous versus intermittent phototherapy in treatment of neonatal jaundice: a randomized controlled trial

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Abstract

Phototherapy (PT) is a widely used treatment for neonatal jaundice, yet the ideal model of application remains controversial. In this study, the effects of continuous phototherapy (CPT) and intermittent phototherapy (IPT) models were compared in the treatment of neonatal indirect hyperbilirubinemia (IHB) and whether IPT is a superior modality is investigated. Single-centre parallel randomized controlled open label trial. A computer-based table of random numbers was used to allocate treatments. Newborns ≥ 34 weeks' gestation who received phototherapy in our neonatal intensive care unit (NICU) between July 2022 and April 2023 were included. CPT was applied continuously for 6 h, and IPT was applied as 2 cycles of 1 h on and 2 h off in a 6-h session. Rebound TSB was measured 8 h after phototherapy was stopped in both groups. Phototherapy duration, TSB reduction rate and rebound bilirubin rate were compared between intervention groups. One hundered and four neonates met the inclusion criteria during the study period. CPT and IPT were each used in 52 newborns. Demographic characteristics of the study groups, including sex, mode of delivery, birth weight, admission weight, age at postnatal presentation, diet, discharge weight, and history of PT in siblings, were similar ($p > 0.05$). The most common cause of IHB in both groups was ABO incompatibility. The median phototherapy time was 12 h (6–15) in the CPT group and 4 h (2–4) in the IPT group ($p < 0.001$). The mean rate of bilirubin decrease was 1.12 ± 0.73 mg/dl/h in those who underwent IPT and 0.51 ± 0.33 mg/dl/h in those who underwent CPT ($p < 0.001$). The mean rebound bilirubin rate 8 h after phototherapy was 0.08 ± 0.28 mg/dl/h in the CPT group, and -0.01 ± 0.17 mg/dl/h in the IPT group ($p = 0.039$). The length of hospital stay was longer in the CPT group ($p = 0.032$). Skin rash, diarrhoea and increased body temperature were less frequent in the IPT group ($p < 0.001$).

Conclusions: In this study, IPT was found to be at least as effective as CPT in reducing total serum bilirubin. Even though the duration of PT is shorter in IPT, the slower rate of rebound bilirubin, shorter hospital stays and lower incidence of side effects indicated that intermittent phototherapy is superior to continuous phototherapy. Choosing IPT over CPT is a more rational approach in neonatal jaundice.

ClinicalTrials.gov Identifier: NCT 06386731 (registered retrospectively on 23/04/2024)

What is Known:
- *PT is common used in the treatment of neonatal jaundice.*
- *There is no standard model of application for PT.*

What is New:
- *The IPT model is as effective as CPT.*
- *Newborns are discharged faster with IPT.*

Keywords Continuous phototherapy · Indirect hyperbilirubinemia · Intermittent phototherapy · Rebound bilirubin

Abbreviations

CPT	Continuous phototherapy
IHB	Indirect hyperbilirubinemia
IPT	Intermittent phototherapy
i Ca	Ionized calcium
NICU	Neonatal intensive care unit
LED	Light emitting diode
PT	Phototherapy
STB	Serum total bilirubin

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Introduction

Indirect hyperbilirubinemia (IHB) is one of the most common causes of hospital admission in newborns. Despite many innovations and improvements with current developing healthcare practices, a significant part of the patients admitted in neonatal intensive care units (NICU) are newborns with IHB [1, 2]. Neonatal jaundice also ranks high among the reasons for readmission to hospital [3, 4]. If severe IHB is not treated early and appropriately, it may result in neurological sequelae [5, 6]. Therefore, neonatal IHB and its treatment remain significant [7–10]. The goal of treatment in neonatal hyperbilirubinemia is to reduce the bilirubin levels safely and quickly. The most common treatment to decrease the bilirubin levels is phototherapy [11, 12]. Although much has been learned about the mechanisms of action, side effects and application techniques of phototherapy since its first use, there are still unanswered questions [13, 14]. In addition to retinal degeneration, DNA damage, and potential genotoxic side effects of phototherapy, temporary side effects including insensible fluid loss, hyperthermia, dehydration, altered stool consistency and frequency, weight loss, and skin rash have also been reported [15]. Reducing exposure time is a rational approach to decrease the side effects of phototherapy [2, 16–18]. One of the unanswered questions in phototherapy is related to the correct method and duration of application, and the mechanism of action of phototherapy can lead to a reasonable answer. The effects of phototherapy occur in two steps, as explained by the in vivo bilirubin photodegradation hypothesis. The first step begins with the bilirubin in the skin absorbing the photon, and the conversion of bilirubin into its water-soluble photoisomers is completed within nanoseconds. In the second step, while bilirubin migrates from the blood pool to the skin, bilirubin photoisomers migrate from the skin to the blood. During this period, the effect of phototherapy is limited. The second stage, bilirubin migration is a slow and rate-limiting process that occurs within a few hours (2–3 h) [19, 20]. Considering the mechanism of action of phototherapy, interrupting phototherapy for the time required for bilirubin migration and then restarting it, which is called intermittent phototherapy (IPT), seems reasonable.

Although phototherapy is the most common treatment in neonatal units, there is no standard practice for its application. Ideal phototherapy should achieve maximum efficiency with minimum exposure time. In this study, the effectiveness of the IPT model, which reduces exposure, and continuous phototherapy (CPT) were compared to determine the ideal phototherapy treatment.

Methods

Study design

This was a single-centre, parallel randomized controlled open label trial.

Participants

The inclusion criteria was being a late preterm or term neonate who had IHB in the first 15 days of life. Newborns with a serum total bilirubin (STB) level measured above the phototherapy threshold according to the nomogram were eligible for treatment [21]. Those who had STB values at the blood exchange limit according to the nomogram, any associated congenital anomalies including chromosomal anomalies, comorbidities or were less than 34th gestational week were excluded.

This study was conducted in a university hospital in Istanbul, Turkey, with a tertiary NICU, where approximately 1500 newborns are treated annually. Newborns who are planned to undergo phototherapy for IHB in the NICU between July 2022 and April 2023 were included in the study. Written informed consent was obtained from the parents of infants who met the inclusion criteria for the study.

Intervention

A computer-based table of random numbers was used to allocate treatments. The treatment protocol was divided into two models according to the duration of phototherapy exposure. In the first model, phototherapy was applied uninterruptedly for 6 h, which was defined as CPT. In the second model, the 1-h on, 2-h off cycle was repeated twice, and phototherapy was on only for 2 h in a 6-h period. This model was defined as IPT. In both models, one phototherapy session was determined as 6 h. Phototherapy duration was automatically controlled by the timer of the device. Serum total bilirubin and ionized calcium (i Ca) levels were measured after phototherapy sessions. There was no cross-over between the groups and the method of phototherapy was not changed until the newborn's STB level fell below the phototherapy threshold in the nomogram. If the patient's STB level fell below the phototherapy threshold according to the nomogram and phototherapy was ceased, STB was checked 8 h later for rebound bilirubin level. Further need for phototherapy was determined according to the rebound bilirubin level and, if necessary, additional sessions were applied. Bilirubin

decrease rate (mg/dl/h) was calculated using the following formula: [STB level before PT (mg/dl) – STB level at the end of the PT session (mg/dl)]/PT time applied in the session (h). Rebound increase rate (mg/dl/h) was calculated with the following formula: [STB value 8 h after the PT session (mg/dl) – STB value at the end of the PT session (mg/dl)]/8 h.

All newborns included in the study received unidirectional phototherapy from a distance of 30–40 cm, with a wavelength of 425–475 nm and a power of 45 watts, using the TENDE® Babyblue LED Phototherapy device (Model No-SN: N-0051, Turkey) in our unit. During phototherapy, only the perineal area of the patients was covered with a reduced size diaper. Infants started phototherapy in the prone position in both groups. The sleeping positions of the neonates were changed during their routine care. The infants' eyes were covered with a three-layer cotton Dilex® black eye patch, which blocks 99.5% of ultraviolet rays.

The infants continued to be fed routinely, 8 times a day at 3-h intervals. Infants in the CPT group were fed by stopping the phototherapy for a maximum of 15 min to minimize the interruption of treatment. It was ensured that this period was not exceeded in babies who were breastfed by their mothers. In the IPT group, feeding times were arranged according to the period when phototherapy was off and there were no restrictions on the feeding time of the infants. In this group, parent-infant bonding was achieved more easily and for a longer period of time.

Serum total bilirubin measurements of all newborns were performed using the capillary method on Siemens RAPIDPoint® 500e Blood Gas System (Serial No: 59,556, Germany).

Blood group and direct Coombs tests were performed with samples taken from the umbilical cord after birth and maternal blood groups and indirect antibody tests were studied by taking 2 ml of blood into an EDTA tube and using gel centrifugation method.

Axillary body temperatures were measured before and after phototherapy by the care provider nurse. Welch Allyn SureTemp® Plus 692 (GTIN: 0073209406242, United Kingdom) electronic thermometer was used in these measurements. Daily body weights were measured with a Seca 334® (ProdID: 5,334,022,210,209, Germany) digital baby scale sensitive to 5 g. The number of daily defecation was checked by the nurses every 2 h. Infants with eight or more stools per day were considered to have diarrhoea. The presence of skin rash was checked by the study coordinator at the end of each phototherapy session.

A case report form was created for each patient. Demographic, clinical and laboratory data of both the neonates and their mothers were recorded in this form.

Outcomes

The primary outcome was to compare the therapeutic efficacy of IPT and CPT. In order to assess the outcome, total phototherapy hours, the rate at which bilirubin levels decrease (mg/dl/h), the rebound bilirubin level as measured 8 h after cessation of phototherapy and the length of hospital stay (days) were compared among the two groups. The secondary outcome was the comparison of phototherapy side effects including hypocalcaemia, increased body temperature, skin rash and increase in stool frequency between the two treatment modalities.

Sample size

According to data obtained from a study investigating the effect of phototherapy on STB decrease, the effect size (Cohen's d) was calculated as 0.578 [22]. The effect size in question was entered into power analysis with a margin of error of 0.05 and power value of 0.80. The power analysis calculations revealed the minimum sample size for our study in order to analyze the bilirubin reduction difference to be 96. The calculation of the estimated the sample size was made using the G*Power 3.1.9.7 software.

Randomization

The patients were divided into two equal groups with a 1:1 allocation ratio using a computer-based random number sequence with a block size of four. Participants enrolled by the study conductor were divided into two groups with serial numbers assigned by the computer. Each patient in both groups was treated with incubator LED phototherapy.

Due to the nature of the intervention, blinding could not be applied.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 18 © Copyright SPSS Inc. 1989, 2010 software. Normality of continuous variables was assessed using Kolmogorov-Smirnov test. Categorical variables were expressed as frequency (n) and percentage (%) while continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR] 25–75). Pearson's chi-squared test, Fisher's exact test and Yates correction were used to analyze categorical variables. Normally distributed data were compared with independent samples *t*-test, while non-normally distributed data were compared with Mann-Whitney *U* test. $p < 0.05$ was considered statistically significant.

Results

During the 10-month study period, 225 (45%) of a total of 498 patients hospitalized in our NICU were treated for neonatal jaundice. Among the 104 newborns who met the study criteria, 52 patients underwent CPT and while the remaining 52 underwent IPT. The study was scheduled to start in July 2022 and end in April 2023. Since the target sample size was reached in this period, the study was terminated on the planned date. The study flow chart is shown in Fig. 1.

Demographic characteristics and laboratory findings at the initial presentation before phototherapy were compared between the groups (Table 1). The mean gestational age was higher in the IPT group than in the CPT group ($p = 0.045$). The mean bilirubin level at the initial presentation was higher in the IPT group than in the CPT group ($p = 0.020$).

The aetiology of neonatal jaundice in infants receiving phototherapy is presented as additional data in Online resource-1. The diagnosis was considered idiopathic in term infants who had no blood group incompatibility, no erythrocyte membrane and enzyme defects, no erythrocyte sequestration on scalp or other organs due to birth trauma, no signs and symptoms of infection and those who did not meet the definition of early and late breast milk jaundice. The most common cause of IHB in both groups was ABO incompatibility.

The clinical and laboratory effects of phototherapy were compared between IPT and CPT models (Table 2). The median duration of phototherapy was significantly longer in the CPT group ($p < 0.001$). Skin rash, diarrhoea and increased body temperature were significantly lower in the IPT group ($p < 0.001$).

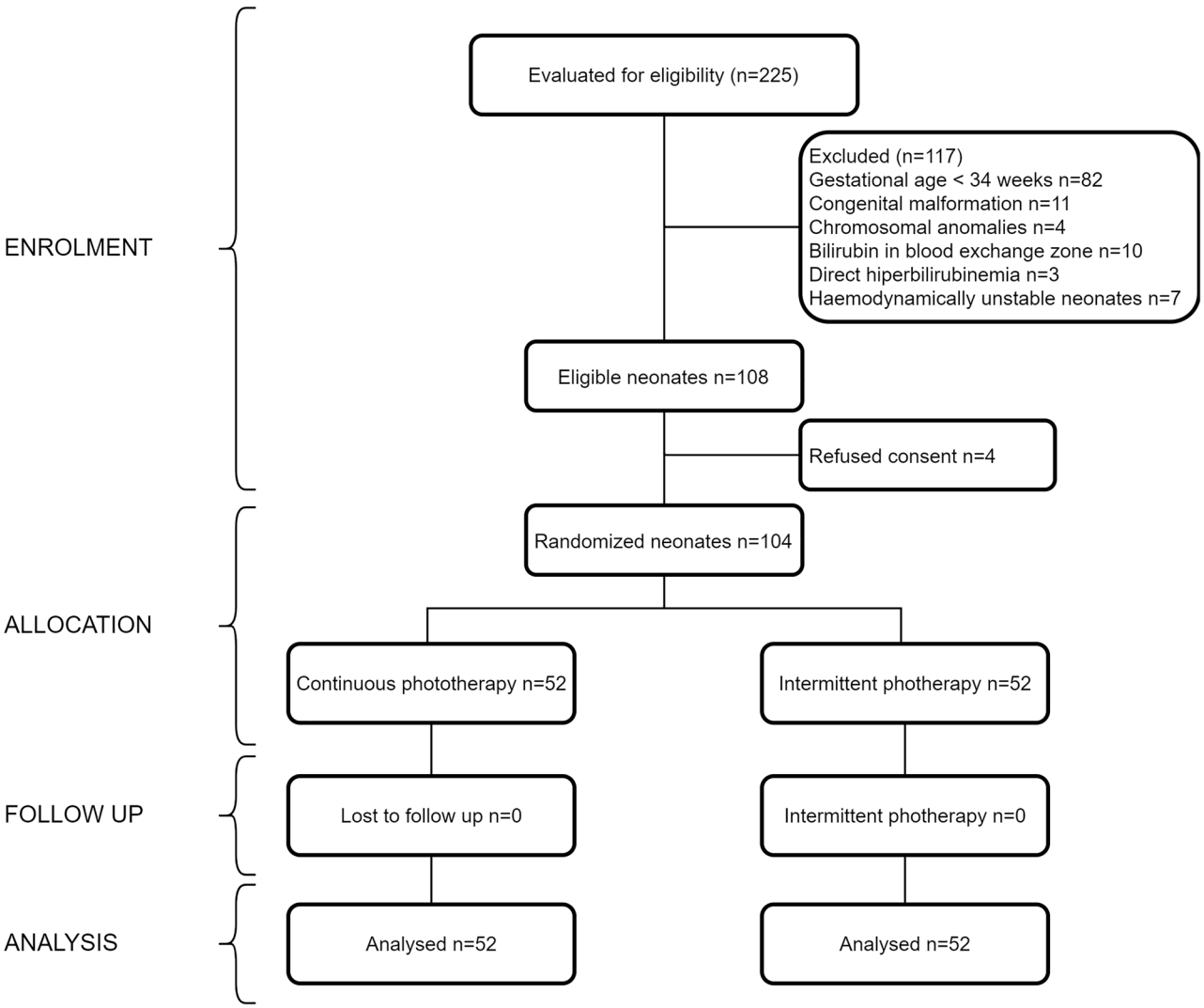

Fig. 1 Consort flowchart showing study design

Table 1 Comparison of baseline variables and demographic characteristics

	CPT group ($n=52$)	IPT group ($n=52$)	p
Maternal characteristics			
Parity			0.299
Primipar	20 (38.5)	15 (28.8)	
Multipar	32 (61.5)	37 (71.2)	
Delivery mode (natural/caesarean)	14/38	23/29	0.065
Maternal blood group O	21 (40.4)	20 (38.5)	0.841
Maternal Rh negative	6 (11.5)	3 (5.8)	0.488
Newborn characteristics			
Gender (female/male)	23/29	30/22	0.170
Gestational age, (week)	37.2 ± 1.8	38 ± 1.4	0.008*
Birth weight, g	3113 ± 657	3216 ± 463	0,359
Direct antibody test (Coombs)	13 (25)	8 (15.4)	0,222
Age at starting PT (day)	3 (2–4)	3 (2–4)	0.418
Previous baby jaundice	19 (36.5)	19 (36.5)	> 0.999
Feeding			0.731
Breast feeding	15 (28.8)	17 (32.7)	
Breast feeding + formula	27 (51.9)	23 (44.2)	
Direct antibody test (Coombs)	13 (25)	8 (15.4)	0,222
STB level before PT (mg/dl)	14.2 ± 3.8	15.9 ± 3.2	< 0.020*
Peak bilirubin level (mg/dl)	14.9 ± 3.3	16 ± 3	0.079
iCa level before PT	1.13 ± 0.12	1.13 ± 0.13	0.897
Body temperature before PT (°C)	36.5 (36.2–36.6)	36.3 (36.1–36.6)	0,413

Data are given as means ± standard deviation, n (%), median interquartile range (IQR)

CPT continuous phototherapy, *IPT* intermittent phototherapy, *PT* phototherapy

*$p < 0.05$

Discussion

CPT is frequently used in the treatment of IHB in newborns. However, the ideal phototherapy model is controversial. Considering the in vivo photodegradation hypothesis, IPT, which provides a break from phototherapy for a certain period of time, can be viewed as an ideal method [19, 20]. However, there is no standard practice in IPT treatment. Different protocols are applied, especially regarding phototherapy on-off time and monitoring of post-phototherapy bilirubin level.

In our study, the phototherapy duration in the IPT group was significantly shorter than in the CPT group ($p < 0.001$). IPT models using different intervals of on and off phototherapy time have been investigated in the literature. Although different phototherapy models are utilized, the duration of phototherapy in IPT was found to be significantly shorter than CPT in most studies as well as a recent

Table 2 Comparison of outcomes among phototherapy models

	CPT group ($n=52$)	IPT group ($n=52$)	p	95% CI of the Difference	OR (with 95%CI)
Outcomes					
Duration of PT (h)	11 ± 6	4 ± 2	< 0.001*	7,53 (5,90 – 9,17)	
STB decrease rate (mg/dl/h)	0.51 ± 0.33	1.12 ± 0.73	< 0.001*	-0,60 ((-0,84)-(-0,36))	
Rebound bilirubin rate (mg/dl/h)	0.08 ± 0.28	− 0.01 ± 0.17	0.039*	0,09 (0,005 – 0,18)	
Hospitalization duration (day)	3 (2–4)	3 (2–3)	0.032*	0,53 (0,08 – 0,99)	
Skin rash n (%)	34 (65.4)	16 (30.8)	< 0.001*		0,235 (0,104-0,534)
Increased stooling > 8 t/day	26 (50)	4 (7.7)	< 0.001*		0,083 (0,026 – 0,265)
Body temperature after PT (°C)	36.7 (36.5–36.8)	36.3 (36.2–36.6)	< 0.001	0,24 (0,13 – 0,35)	
iCa level after PT	1.17 (1.09–1.25)	1.14 (1.09–1.27)	0.699	-0,001 ((-0,05)-(0,05))	

Data are given as means ± standard deviation (SD), n (%), median interquartile range (IQR)

CPT continuous phototherapy, *IPT* intermittent phototherapy, *PT* phototherapy, *CI* confidence interval, *OR* odds ratio

meta-analysis [17, 23–26]. On the other hand, in their randomized controlled clinical study, Gottimukkala et al. [27] found out that the total duration of phototherapy was similar in both groups. In their study, bilirubin levels were re-assessed at standard 12-h intervals in both groups, and the decision to terminate phototherapy was made according to control STB levels. Therefore, STB falling below the phototherapy threshold in the IPT group may not have been detected at the earliest time, and the duration of phototherapy may have been extended unnecessarily. This may explain the similar duration of phototherapy hours in the two groups of the study.

The rate of bilirubin reduction is an important indicator of the therapeutic efficacy of phototherapy. In the current study, the rate of bilirubin decrease as calculated according to the time under phototherapy was significantly higher in the IPT group. This data shows that IPT is at least as effective as CPT in reducing bilirubin despite shorter total exposure time. The rate of bilirubin decrease was found to be similar in models using different phototherapy durations in the currently available published data [23–27]. A meta-analysis published in 2023 compared intermittent and continuous phototherapy in terms of therapeutic effectiveness. In this meta-analysis, there was little or no difference between intermittent phototherapy and continuous phototherapy with respect to the rate of decline in bilirubin levels in jaundiced newborns [28].

The effect of phototherapy models on early rebound bilirubin level observed in our study is an important data because patients with a high rebound bilirubin level are predicted to require further phototherapy sessions, thus longer hospital stay. IPT offers a time period that allows for photoisomers to be cleared away from the skin and bilirubin migration from the bloodstream to the skin [19, 20]. In the intermittent model, a better bilirubin clearance can be achieved by gradual and balanced displacement of bilirubin while phototherapy is off. On the contrary, when the continuous radiation is suddenly ceased in CPT, the amount of bilirubin that migrates to the skin due to the load of bilirubin metabolites that need to be excreted may cause a sudden rebound increase. In the current study, infants in the IPT group did not experience rebound bilirubin increases, which contributed to earlier discharge. A study in the literature reported no differences between the bilirubin measurements at 24th, 48th and 72nd hours after intermittent and continuous PT [24]. However, we could not find any study in the literature regarding the effect of different phototherapy models on rebound bilirubin increase with similar timings to our study.

The length of hospital stay in our patients was shorter in the IPT group than in the CPT group. This is in parallel with the shorter duration of phototherapy and is a supporting factor for the effectiveness of IPT. However, studies in the literature report similar lengths of hospital stay between groups receiving intermittent and continuous phototherapy [23, 24]. The reason for this may be that the duration of phototherapy is chosen longer in the IPT protocol. The phototherapy model, which is not conducive to early discharge, may have masked the effect of IPT on hospital stay.

The secondary outcome of our study was the comparison of acute side effects among phototherapy models. We compared i Ca levels in both groups to evaluate hypocalcaemia as a side effect of phototherapy. The mean i Ca levels of our patients at baseline and at the end of phototherapy were similar in both groups. Hypocalcaemia was not observed in either group. The effects of phototherapy on calcium metabolism are explained with various mechanisms in the literature [29, 30]. Preterm infants are more prone to hypocalcaemia and their bone metabolism is affected more by phototherapy [31]. Our patients were not in the risky premature infant's category and we did not identify any negative effects of phototherapy on Ca metabolism. Anyway, phototherapy-related hypocalcaemia is very rarely clinically evident and resolves spontaneously within 24 h after PT is discontinued [32].

An increased duration of phototherapy is known to lead to a higher frequency of skin rash, diarrhoea and increased body temperature [24, 27]. Our results showed that acute transient adverse effects of phototherapy including skin rash, diarrhoea and increased body temperature were observed to be significantly higher in the CPT group. The heat emitted by light sources increases the environmental temperature. LED phototherapy devices are known to emit less heat to the environment than conventional phototherapy devices. However, a 2011 Cochrane meta-analysis reported that the risk of hyperthermia between LED and conventional phototherapy devices was similar [33]. All patients in our study received LED phototherapy. Increased body temperature as an acute side effect of phototherapy can have various underlying mechanisms. Hyperthermia is a result of increased irradiance rather than the type of light source of phototherapy [34]. Second, hyperthermia can be explained by the impact of phototherapy light on the release of pyrogenic cytokines [35]. The increased exposure time in the CPT group explains the elevated body temperature due to the increase in the irradiance of light and thus, pyrogenic cytokines. It has been reported in the literature that long-term exposure to phototherapy for the treatment of IHB increases its side effects, and therefore, treatment should be carried out for the shortest time and with the least amount of radiation [2, 15–18, 23, 24, 27, 36]. Shorter duration of phototherapy that the infants are exposed to, and fewer side effects indicate that IPT is safer. No harmful effects were observed in the intervention group, IPT.

This study has some limitations. First, this is a single-centre study with relatively limited number of patients. Another limitation was that the gestational age of newborns in the CPT group was less than those in the IPT group despite randomization. However, since the birth weight of the babies in both groups

was similar, this difference might be of negligible relevance. The mean STB level of the IPT group before phototherapy was higher than the CPT group. However, this difference did not change indications to start phototherapy according to Bhutani nomogram. Lastly, bilirubin levels were measured in the serum in our study which can be considered a more invasive method in comparison to transcutaneous measurements. Although transcutaneous bilirubin measurement is known to be as reliable as serum values [37–39], we preferred to study serum levels because of our technical infrastructure.

Conclusion

The results of this study showed that our intermittent model was quite effective in reducing STB despite shorter time of phototherapy. Due to the positive effect of our model of IPT on rebound bilirubin levels, patients can be discharged faster. The unwanted phototherapy side effects were observed less in the IPT group. Our study showed the defined model of IPT is not only effective but also safe in the treatment of neonatal jaundice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-024-05610-7.

Author contributions H N. D. and S S. O. prepared the materials and collected the data. S S. O. and H F. O. analyzed the data, interpreted them and created figures. H N. D. and S S.O. wrote the first draft of the article. H F. O. made criticisms. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Ethics approval The study was approved by the local ethics board in concordance with the Declaration of Helsinki. Ethics committee approval was obtained from the Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee dated 15 June 2022 (decision number 2022/0387).

Consent to participate Written informed consent was obtained from the parents of newborns.

Competing interests The authors declare no competing interests.

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