THE INFLUENCE OF PHOTOTHERAPY HEMOGLOBIN LEVEL ON THE EFFICACY OF IN NEONATAL JAUNDICE

By

Mahmoud Mohammed Abdo[1], Ahmed Helal EL-Sayed[1], Ahmed Saad El-Deen Ibrahim[1], Ahmed Anwar Shaheen[2]

[1]Pediatrics and [2]Clinical pathology department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

***Corresponding author:** Mahmoud Mohammed Abdo

Mobile: (+02) 01115134533, **Email:** ma1258973@gmail.com

ABSTRACT

Background: *Red blood cell breakdown creates bilirubin. Red cell breakdown creates unconjugated (indirect) bilirubin, which circulates mostly bound to albumin although some is free and hence able to enter the brain. Unconjugated bilirubin is metabolized by the liver to conjugated bilirubin then excreted in stool. Since the 1960s, phototherapy has treated neonatal hyperbilirubinemia. The treatment has improved as the light sources and strategy for using these have been optimized. Phototherapy replaces exchange transfusions due to its efficacy and safety. Phototherapy changes native, non-polar, and neurotoxic Z,Z-bilirubin to more polar isomers called photo bilirubins, which consist of Z,E- and E,Z-bilirubin and E,Z- and E,E-lumirubin. Hemoglobin and bilirubin compete for light absorption.*

Aim of the study: *This study aimed to assess the influence of hemoglobin level on the efficacy of phototherapy for treating neonatal jaundice in neonates.*

Subject and Methods: *This is a prospective observational study carried out on 100 neonates with pathological indirect hyperbilirubinemia. This study had been done at AL-Hussein University Hospital, in the period from February 2022 to October 2022.*

Results: *Our study results showed that hematocrit levels ranged from 25 to 68 with mean ± SD = 44.14 ± 7.55. Hemoglobin levels ranged from11.5 to 20.5 with mean value of 14.12 ± 1.04 gm/dl. There was a statically significant negative correlation according to Pearson's correlation coefficients (r) between total serum bilirubin concentration change after 24 h of phototherapy and hemoglobin levels.*

Conclusion: *We concluded that hemoglobin had a significant effect on the efficacy of phototherapy: the higher the hemoglobin concentration, the smaller the decrease in TSB. This knowledge is important for clinicians who treat hyperbilirubinemic infants with phototherapy.*

Key Words: *Hemoglobin, Phototherapy, Neonatal Jaundice.*

INTRODUCTION

Jaundice is one of the most common conditions needing medical attention in newborn babies. Jaundice refers to the yellow discoloration of the skin and the sclera caused by accumulation of bilirubin in the skin and mucous membranes. Jaundice is caused by a raised level of bilirubin in the body, a condition known as hyperbilirubinemia **(Ansong-Assoku et al., 2022)**.

Approximately 60% of term and 80% of preterm babies develop jaundice in the first week of life, and about 10% of breastfed babies are still jaundiced at 1 month **(Mohamed Tawfik et al., 2022)**.

Bilirubin is mainly produced from the breakdown of red blood cells. Red cell breakdown produces unconjugated (indirect) bilirubin, which circulates mostly bound to albumin although some is free and hence able to enter the brain. Unconjugated bilirubin is metabolized in the liver to produce conjugated (direct) bilirubin which then passes into the gut and is largely excreted in stool. The terms direct and indirect refer to the way of the laboratory tests **(Anderson & Calkins, 2020)**.

Over the last 50 years, phototherapy has been used to treat neonatal hyperbilirubinemia to prevent extremely high levels of bilirubin that may cause bilirubin-induced encephalopathy **(Ansong-Assoku et al., 2022)**.

The treatment has improved as the light sources and strategy for using these have been optimized. Exchange transfusions have increasingly replaced by phototherapy because of both the efficacy and the superior safety profile of the latter **(Donneborg et al., 2017)**.

It is well known that phototherapy transforms unconjugated bilirubin from the native, non-polar, and neurotoxic Z,Z-bilirubin to more polar isomers called photo bilirubins that consists of introduction configurationally isomers Z,E- and E,Z- bilirubin and structural isomers E,Z- and E,E-lumirubin. These isomers can then be excreted without conjugation into the bile and the structural isomers into the urine **(Langah et al., 2019)**.

Whether the biochemical processes during phototherapy occur predominantly intra-vascularly or extra-vascularly has long been debated, although recent evidence strongly supports the idea that the biochemical processes during phototherapy predominantly take place intra-

vascularly. In vitro studies, it has also found that hemoglobin is a major competitor with bilirubin for the absorption of light during light exposure. It was predicted that a high hematocrit would reduce the therapeutic efficacy of phototherapy **(Donneborg et al., 2017)**.

AIM OF THE STUDY

The aim of this study is to assess the influence of hemoglobin level on the efficacy of phototherapy for treating neonatal jaundice in neonates admitted into the neonatal intensive care unit (NICU) of AL-Hussein University Hospital.

Ethical consideration:

1. An informed consent was obtained from parents or legal guardians before getting involved in the study.
2. The study was done after approval of ethical committees of Pediatrics department and faculty of medicine for Al-Azhar University.
3. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
4. All the data of patients and results of the study are confidential and the patients have the right to keep it.
5. The parents have the right to withdraw from the study at any time without giving any reasons.

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PATIENTS AND METHODS

Sample size calculation:

The sample size was calculated using Power and Sample size software version 3 (epi info). The sample size was calculated using the following formula:

$$n = 2\left[\frac{\left(Z_{\alpha/2} + Z_{\beta}\right) * \sigma}{\mu_1 - \mu_2}\right]^2$$

By calculation, the sample size will be equal to 100 in total.

This is a prospective observational study conducted at the neonatal intensive care unit of AL-Hussein University Hospitals. The study is carried out on 100 neonates with indirect hyperbilirubinemia. That was done in the period from February 2022 to October 2022. The patients selected by simple random method.

Inclusion criteria:

a. Healthy full term and late preterm neonates with indirect hyperbilirubinemia requiring phototherapy according to hour-specific bilirubin nomogram.

b. No sign for hemolytic disease.

c. Birth weight must be more than 1800g.

d. Postnatal age should be more than 24h but less than 10 days.

e. Those that were not previously exposed for phototherapy.

Exclusion criteria:

a. Gestational age < 34 weeks.

b. Direct hyperbilirubinemia.

C. Presence of a neonatal illness other than jaundice such as sepsis and metabolic diseases.

d. Previous treatment with phototherapy.

All patients were subjected to the following:

I. Careful history taking regarding:

Prenatal history including: maternal age, maternal blood group, gestational diabetes, gestational hypertension, pre-eclamsia, anemia during pregnancy, maternal infection and fever.

Natal history with stress on: mode of delivery, single or multiple pregnancies, prolonged labor, birth trauma, asphyxia, need for resuscitation.

Postnatal history with emphasis on:

- Onset of jaundice.
- Type of feeding.
- Adequacy of breast feeding.
- Presence of cephal-hematoma and bruising.
- Presence of IUGR.

Family history:

- Previous sibling with jaundice in the neonatal period.
- Previous sibling who needed phototherapy.
- Family members or known heredity for hemolytic disorders like G6PD and spherocytosis.

II. Thorough clinical examination including:

Complete general examination:

- Vital signs: heart rate, respiratory rate, Temperature, pulse oximetry.
- Complexion: Jaundice, pallor or skin rash.

Abdominal examination: For hepatosplenomegaly.

Chest examination: For signs of respiratory distress.

Cardiac examination: Signs of heart failure due to severe hemolytic disease or septic shock.

Neurological examination:

1. Neonatal reflexes
2. Signs of kernicterus such as seizures, hypotonia, hypertonia, opisthotonos and retrocollis.

III. Laboratory evaluation including:

1. Serum bilirubin (total and direct) by (Biolis 50i Superior).

At admission and after 24hrs of admission.

- Delta bilirubin (TSBΔ): which is the difference between total bilirubin at admission (TSB0) and total bilirubin after 24hr of phototherapy (TSB24). TSBΔ = TSB0 - TSB24

2. Complete blood count by (Sysmex XN-350) with stress on Hb(gm/dl) and Hct

At admission and after 24hrs of admission.

3. Quantitative c- reactive protein to exclude sepsis.
4. Reticulocyte count.
5. Rh and blood grouping for mother and babies.
6. Coombs test: direct and indirect Coombs test.

Phototherapy: conventional phototherapy equipment containing blue LED lamps with wave length of 400-500 nm, is placed at a distance of 30-40 cm, light irradiance was 60 (µW/cm2/nm). Phototherapy was continuous except at time of feeding.

Statistical analysis:

All data were collected, tabulated and statistically analyzed using SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median.

Qualitative data is expressed as number and percent.

Normally distributed variables will be presented as mean and standard deviation while non-normally distributed quantitative data will be presented as median and interquartile range. Wilcoxon signed rank test was used to compare paired samples (e.g., bilirubin level before and after phototherapy).

Chi-square test or Fisher exact test will be used to assess association between qualitative variables.

The used tests were:

- **Pearson correlation coefficient:** used to measure the strength of a relationship is between two variables.

RESULTS

The results of our study summarized in the following tables and figures:

Table (1): Demographic and clinical data of the studied neonates

		Study population (n = 100)
Gender	Male	52
	Female	48
Gestational Age (weeks)	Mean ± SD.	36.77 ± 2.08
	Median (IQR)	37 [3]
	Range (Min-Max)	34 – 40
Postnatal age (hours)	Mean ± SD.	114.98 ± 24.05
	Median (IQR)	113 [12]
	Range (Min-Max)	26 – 217
Birth weight (Kg)	Mean ± SD.	3.01 ± 0.52
	Median (IQR)	3.2 [0.9]
	Range (Min-Max)	1.9 – 4

SD: standard deviation, IQR: interquartile range

This table shows the demographic and clinical data of the studied neonates.

Table (2): Laboratory findings of the studied neonate at the start of phototherapy

		Study population (n = 100)
Hemoglobin level (gm/dl)	Mean ± SD.	**14.12 ± 1.04**
	Median (IQR)	**14.2 [1.2]**
	Range (Min-Max)	**11.5 – 20.5**
Hematocrit (%)	Mean ± SD	**44.14 ± 7.55**
	Median (IQR)	**44.5 [5]**
	Range (Min-Max)	**25 – 68**
Total bilirubin (mg/dL)	Mean ± SD.	**17.12 ± 2.98**
	Median (IQR)	**17.05 [3]**
	Range (Min-Max)	**14 – 21**

SD: standard deviation, IQR: interquartile range

Table (3): Laboratory findings of the studied neonates after 24hrs of phototherapy

		Study population (n = 100)
Hemoglobin level (gm/dl) after 24 hrs of phototherapy	**Mean ± SD.**	**13.99 ± 1.01**
	Median (IQR)	**13.88 [1.2]**
	Range (Min-Max)	**11.4 – 20.2**
Hematocrit (%)after 24hrs of phototherapy	**Mean ± SD**	**43.88 ± 7.25**
	Median (IQR)	**43.9 [5]**
	Range (Min-Max)	**24 – 67**
Total bilirubin after 24 hrs of phototherapy (mg/dL)	**Mean ± SD.**	**14.02 ± 2.34**
	Median (IQR)	**14.2 [2]**
	Range (Min-Max)	**8 – 17**

SD: standard deviation, IQR: interquartile range

Table (4): Comparison between initial and 24hrs total serum bilirubin levels of neonates

variable	patients	p-value
Initial total serum bilirubin level (mg/dl)	**17.05 [3]**	**<0.001**
24 hrs. total serum bilirubin level (mg/dl)	**14.2 [2]**	

Data is expressed as median (interquartile range)

This table shows that total serum bilirubin 24hrs after admission was significantly lower than the admission levels.

Table (5): Serum bilirubin level change after 24 h of phototherapy (∆TsB) among the study population

		Study population (n = 100)
Serum bilirubin level change after 24 h of phototherapy (∆TsB) (mg/dL)	Mean ± SD.	**3.49 ± 2.34**
	Median (IQR)	**3.5 [1.5]**
	Range (Min-Max)	**0.5 – 6**

SD: standard deviation, IQR: interquartile range

Table (6): Pearson's correlation coefficients (r) between serum bilirubin concentration change after 24 h of phototherapy and hemoglobin concentration

	bilirubin concentration change after 24 h of phototherapy (ΔTsB)	
	R	**P**
Hemoglobin concentration	**-0.682**	**<0.001**
hematocrit level	**-5.894**	**<0.001**

Table (6) showed statistically significant negative correlation between hemoglobin and hematocrit level and the decline in bilirubin concentration after 24 h of phototherapy (ΔTsB).

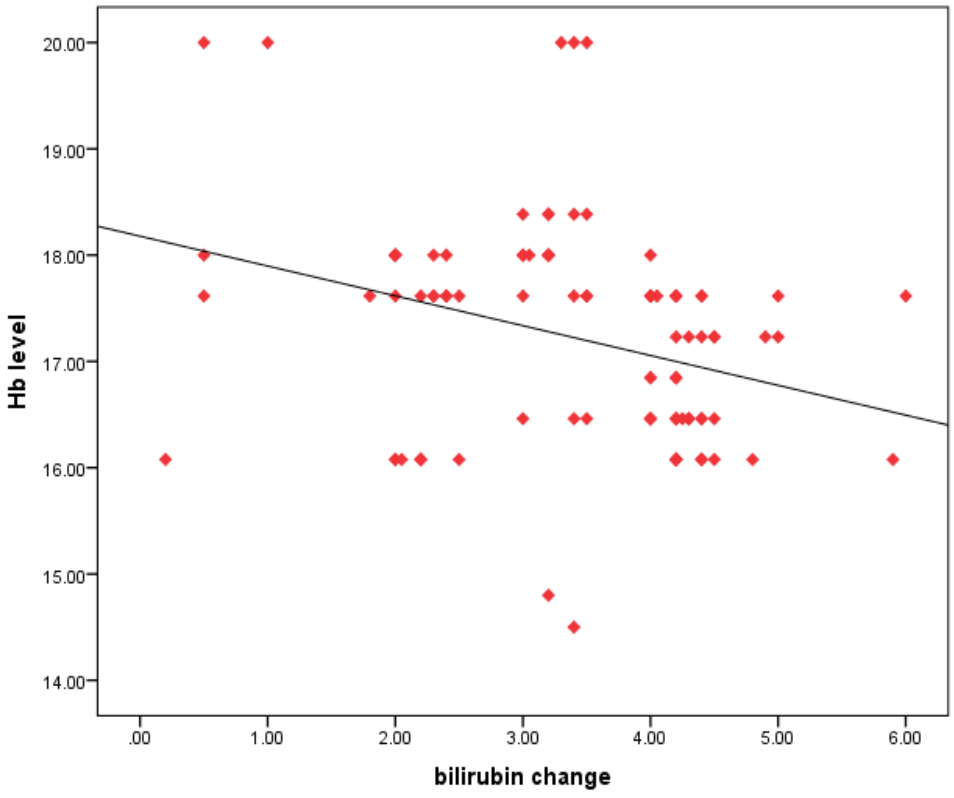

Figure (1): correlation between bilirubin concentration change after 24 h of phototherapy and hemoglobin concentration

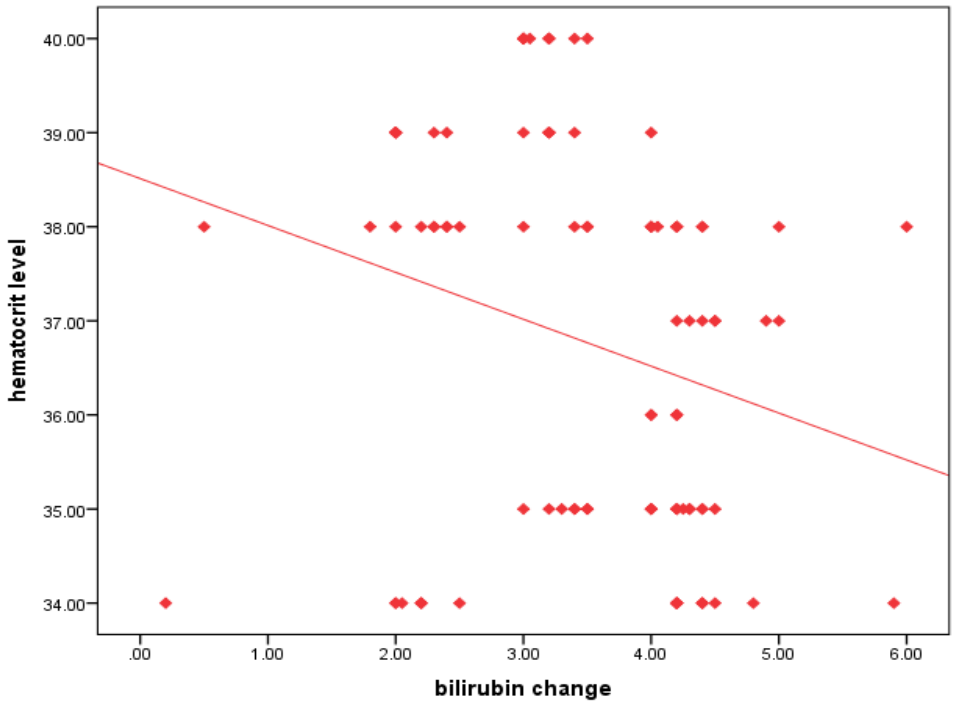

Figure (2): Correlation between bilirubin concentration change after 24 h of phototherapy and hematocrit concentration

DISCUSSION

Neonatal jaundice is not an uncommon condition; approximately 2% - 6% of affected neonates require treatment. Over the past few decades, phototherapy is the treatment of choice for neonatal hyperbilirubinemia, beside intravenous immune globulin (IVIG) and exchange transfusion. Phototherapy prevents the bilirubin to touch the extremely high levels in turn, preventing kernicterus (encephalopathy due to high levels of bilirubin) **(Ebbesen et al., 2017)**.

The mechanism of action of phototherapy is that it converts the unconjugated bilirubin from polar and neurotoxic Z-Z-bilirubin to the more polar form known as photo bilirubin. This transformed photo bilirubin consists of configurational Z-E and E-Z-bilirubin isomers and structural E-Z and E-E-lumirubin isomers. These transformed isomers are easy to excrete in both bile without undergoing conjugation and in urine as well **(Ebbesen et al., 2016)**.

In vitro number of studies reported that hemoglobin competes the bilirubin for absorbing light during phototherapy as the erythrocytes do not have nuclei or other cellular organelles so act as the main light absorber **(Linfield et al., 2016)**.

It has been hypothesized that high level of hemoglobin or hematocrit interfered in the effectiveness of phototherapy and only one of the studies confirmed it in vivo **(Donneborg et al., 2017)**.

The main aim of this study was to assess the influence of hemoglobin level on the efficacy of phototherapy for treating neonatal jaundice in neonates admitted into the neonatal intensive care unit of AL-Hussein University Hospitals.

This prospective observational study was conducted at the neonatal intensive care unit of AL-Hussein university Hospital. The study is carried out on 100 neonates with indirect hyperbilirubinemia who are indicated for phototherapy according to hour specific bilirubin nomogram according to (gestational age - post natal age – weight) **(Muchowski, 2014)**.

As regard gender distribution among the study population, male patients was 52 (52%) and female patients were 48 (48%). Gestational age ranged from 34 to 40 weeks with mean value of 36.76 ± 2.08 weeks. While post natal age in the study population ranged from 26 - 217 hours with mean value of 114.98 ± 24.05 hours.

Our results were supported by study of **Donneborg et al., 2017** as they reported that they conducted on 93 infants, with gestational age ≥ 33 weeks, with uncomplicated hyperbilirubinemia. The infants were treated with conventional phototherapy using LED light for 24 h. 48 of them were males. The mean gestational age was 269 (239–293) days and the mean postnatal age was 78 (41–164) hours.

Also, in the study of **Langah et al., 2019**, a total of about 306 participants were included in the study but after excluding, those neonates whose parents refuse to give consent or having unsatisfactory results or developed complications, about 296 participants were finally analyzed. Majority of study participants were male (60.8%), with mean postnatal age of 4.66 ± 1.65.

Birth weight among the study population ranged from 1.9 to 4 kg with mean value of 3.01 ± 0.52 kg.

Our results were supported by the study of **Donneborg et al., 2017**, as they reported that the mean Birth weight of their studied cases was 3,270 (1,835–5,090) (g).

Where in the study of **Langah et al., 2019**, their studied group had mean birth weight of 2.41 ± 0.41 kg.

In our study light irradiance among the study population was 60 (µW/cm2/nm), while in the study of **Donneborg et al., 2017**, the mean light irradiance, measured 71.8 (48.9–84.0) (µW/cm2 /nm) and the mean of Adjusted light irradiance 66.8 (45.5–78.1) (µW/cm2 /nm). Also, in the study of **Langah et al., 2019**, the mean measured light irradiance was 71.8 ± 11.45 with ranges 48.9 - 83.5 (µW/cm2/nm).

In the study of **Ebbesen et al., 2017**, they revealed that phototherapy lights with an emission spectrum of 460-490 nm provide the most efficient bilirubin-reducing light. LEDs should replace fluorescent tubes and halogen spotlights as the preferred light sources.

The present study showed that hemoglobin levels in the study population ranged from 11.5 to 20.5 gm/dl with mean value of 14.12 ± 1.04 gm/dl.

Our results were supported by the study of **Langah et al., 2019**, as they reported that the mean value of hemoglobin was 16.59 ± 2.7.

Where in the study of **Donneborg et al., 2017** they reported that the hemoglobin ranged from 7.0 to 14.7 mmol/l, median 12.0 mmol/l.

In our study, the hematocrit levels among the study population ranged from 25 to 68 with mean ± SD = 44.14 ± 7.55. In the study of **Langah et al., 2019** reported that the mean hematocrit of their studied group was 45.78 ± 6.18 with range 33.42 - 58.14 (%).

Our results showed that as regard total serum bilirubin concentration at the start of phototherapy (TsB0) ranged from 14 to 21 gm/dl with mean value of 17.12 ± 2.98 gm/dl.

Regarding Total serum bilirubin concentration after 24 h of phototherapy (TsB24) ranged from 8 to 17 mg/dl with mean value of 14.02 ± 2.34 gm/dl.

Regarding Serum bilirubin level change after 24 h of phototherapy (ΔTsB) ranged from 0.5 to 6 mg/dl with mean value of 3.49 ± 2.34gm/dl.

Our results were supported by the study of **Langah et al., 2019**, as they reported that at the time of diagnosis, the mean TsB0 was 16.2 ± 6.92. After giving phototherapy for 24 hours, the mean TsB24 was 13.15 ± 3.76, so the ΔTsB0-24 concentration during 24 hours of phototherapy was 5.21 ± 3.05.

In the study of **Donneborg et al., 2017**, the median TsB decrease was 121 μmol/l after 24 h of phototherapy (the mean TsB0 was 270 (181–338), the meanTsB24 was146 (52–209), the meanΔTsB0–24 was 121 (57–199) μmol/l).

In our study there was a statistically significant negative correlation between total serum bilirubin concentration during 24 h of phototherapy and both hemoglobin concentrations and hematocrit levels by using the pearson's correlation coefficients (r). The higher the hemoglobin and hematocrit concentration, the smaller the decrease in (TsB).

In accordance with our results, **Donneborg et al., 2017** showed that the efficacy of phototherapy was significantly dependent on the concentration of hemoglobin. every 1.0 mmol/l increase in hemoglobin concentration leads to decrease in TSB after 24 hrs of phototherapy by 3.61 μmol/l.

In vitro study done, by **Lamola et al. 2013** using a semi empirical skin model, it was confirmed that hemoglobin in the skin competes with bilirubin for absorption of light during phototherapy. This was strongest at the wave length 400– 460 nm, also found in vitro by **Linfield et al., 2016**. On the basis of these results, it was predicted that a high hematocrit would reduce the therapeutic efficacy of phototherapy in vivo.

The clinical observation that the yellow color of the skin in the jaundiced infant diminishes during the first hours of phototherapy had led to the understanding that transformation of Z, Z bilirubin to photobilirubins mainly takes place extra-vascularly in the skin. Pursuant to this understanding, infants in phototherapy were routinely alternated from prone to supine position to increase the efficacy of phototherapy. However, this routine was largely discontinued when it was found that the efficacy of phototherapy is independent of alternating the position of the infant. Other observations also support the hypothesis that the effect of phototherapy is predominantly intravascular. Thus, 15 min after phototherapy is initiated; a substantial amount of the photobilirubin Z, E bilirubin can be measured in plasma, corresponding to 10% of total

bilirubin. This finding seems inconsistent with diffusion from the extravascular to the intravascular compartment, as diffusion is a much slower process **(Bhethanabhotla et al., 2013)**.

Our finding of an inverse relationship between hemoglobin and the efficacy of phototherapy could be explained by an intravascular effect of phototherapy on bilirubin isomerization. The hemoglobin in the erythrocytes will absorb light, which implies that a fraction of the light will not reach the bilirubin molecules, i.e., hemoglobin in the erythrocytes will compete with the bilirubin molecules and thereby influence the efficacy of phototherapy. This has also been investigated by measuring the photo-bilirubins. The formation of Z,E-bilirubin is reversible, and Z,E-bilirubin accumulates rapidly in plasma at commonly used levels of irradiance because of a fast formation and a slow excreting rate. Within a few hours of phototherapy, the ratio of Z,E-bilirubin to Z,Z-bilirubin reaches a plateau, which means that a photo-equilibrium occurs between these two substances **(Lamola, 2016)**.

Mreihil et al. 2015 compared the rate and level of 4Z, 15E photo isomerization during intensive phototherapy and analysis of hemoglobin data from 36 of their patients. They found a significant, negative correlation between hemoglobin concentration and percentage of Z, E-bilirubin after 15, 30, and 60 min; however, it disappeared at the later time points. This was explained by the fact that when an equilibrium between Z, Z-bilirubin and Z, E-bilirubin is obtained in plasma, the percentage of Z, E-bilirubin only depends on the emission spectrum of the light, and is independent of the irradiance. The authors concluded that the hemoglobin concentration would influence the efficacy of phototherapy until equilibrium between Z, Z- and Z, E-bilirubin occurs. However, we found an effect of hemoglobin on the bilirubin decline in plasma after 24 h of phototherapy. We suggest that this is explained by the fact that the production of E, Z lumirubin is the most important bilirubin-lowering process during intensive phototherapy, and equilibrium between E, Z-lumirubin and Z, Z-bilirubin does not occur **(Okada et al., 2005**, **Lamola, 2016)**.

Therefore, the decline of bilirubin is dependent on hemoglobin concentration throughout the whole treatment period and not just during the first 60 min, as shown by **Mreihil et al., 2015**.

In the study of **Langah et al., 2019**, considering Pearson correlation, the hemoglobin had significant inverse association with ΔTsB0-24 while

birth weight and postnatal age also had inverse association but p-values were non-significant. It displayed a very weak negative correlation which might be evident of the fact that increases in hemoglobin concentration resulting in minimal change in total serum bilirubin concentration during phototherapy.

In addition, **Ebbesen et al., 2017** stated that it appears that the photo isomers of bilirubin are predominantly formed in the plasma, and the rate of formation is affected by the hemoglobin concentration.

From a clinical point of view, the current study is important for the physician in treating neonates with hyperbilirubinemia by using phototherapy. Neonates having high hemoglobin concentration need phototherapy for longer duration, with higher light irradiance and larger exposure of body surface-area as compared to neonates with lower concentration of hemoglobin.

CONCLUSIONS

From our results we concluded the following:

1. There was negative correlation between decrease of total serum bilirubin concentration after 24 hrs of phototherapy with hemoglobin concentrations and hematocrit levels.
2. The higher the hemoglobin and hematocrit concentration, the smaller the decrease in TsB.

Recommendation

1. Neonates with high hemoglobin concentration must be exposed for phototherapy for longer duration, with higher light irradiance and larger exposure of body surface-area.
2. Further multicenter studies with larger sample sizes are needed to confirm the current result.
3. Continues follow up of TSB and hemoglobin concentrations in neonates under phototherapy.

LIMITATIONS

1. Limited numbers of studied neonates.
2. Difficulties in repeated sampling from studied neonates.

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