

Phototherapy-Related Transient Direct Hyperbilirubinemia

Fototerapi İlişkili Geçici Direkt Hiperbilirubinemi

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ABSTRACT

Objective: We aimed to investigate the frequency and possible risk factors of phototherapy-related direct hyperbilirubinemia.

Material and Methods: We scanned the medical records of 1301 patients who were admitted to the neonatology unit for indirect hyperbilirubinemia between 2005 and 2013. Infants with a clinical condition other than hyperbilirubinemia were excluded.

Results: Following phototherapy both the direct bilirubin level and direct bilirubin/total bilirubin ratio increased ($p < 0.001$ and $p < 0.001$, respectively). The frequency of phototherapy-related direct hyperbilirubinemia was found to be 0.9% if the direct bilirubin/total bilirubin cut-off level was set to 20%. The elevated direct bilirubin level and direct bilirubin/total bilirubin ratio returned to normal within three days, although they were still significantly higher than the pre-phototherapy levels ($p < 0.001$; $p < 0.001$, respectively). The increase in direct bilirubin level and direct bilirubin/total bilirubin ratio were found to be brisker in patients with ABO incompatibility ($p < 0.001$ and $p < 0.001$, respectively).

Conclusion: The direct bilirubin level and direct bilirubin/total bilirubin ratio may temporarily rise following phototherapy. This deviation is short term, and ABO incompatibility is the only identified risk factor. To prevent unnecessary investigations this phenomenon should be kept in mind by the physicians caring for infants.

Key Words: Adverse events, Hyperbilirubinemia, Newborn, Phototherapy

ÖZET

Amaç: Çalışmamızı fototerapi ilişkili direkt hiperbilirubineminin sıklığını ve olası risk faktörlerini saptamak amacıyla planladık.

Gereç ve Yöntemler: Yenidoğan ünitesine indirekt hiperbilirubinemi tanısı ile 2005 ve 2013 yılları arasında yatan 1301 yenidoğanın dosyaları geriye dönük olarak tarandı. Hiperbilirubinemi haricinde başka hastalığı da olan yenidoğanlar çalışmadan çıkartıldı.

Bulgular: Fototerapiyi takiben hem direkt bilirubin seviyesi hem de direkt bilirubin/total bilirubin oranı artmaktadır (sırasıyla $p < 0.001$ ve $p < 0.001$). Patolojik direkt bilirubin/total bilirubin sınırı %20 alındığında, fototerapi ile ilişkili direkt hiperbilirubinemi sıklığı %0.9 olarak bulundu. Artmış direkt bilirubin seviyeleri ve direkt bilirubin/total bilirubin oranı 3 gün içerisinde normale dönmekteydi, fakat bu değerler halen fototerapi öncesindeki değerlere göre anlamlı olarak yüksekti (sırasıyla $p < 0.001$ ve $p < 0.001$). ABO uyumsuzluğu olan hastalarda direkt bilirubinindeki ve direkt bilirubin/total bilirubin değerindeki artışın daha hızlı olduğu saptandı (sırasıyla $p < 0.001$ ve $p < 0.001$).

Sonuç: Fototerapi sonrasında direkt bilirubin düzeyi ve direkt bilirubin / total bilirubin oranı geçici olarak artabilmektedir. Bu durum kısa sürelidir ve saptanabilen tek risk faktörü ABO uyumsuzluğudur. Gereksiz ileri araştırmaların önüne geçilmesi açısından yenidoğanların tedavisinde görev alan doktorların bu durumu akılda tutmaları yararlı olacaktır.

Anahtar Sözcükler: Yan etki, Hiperbilirubinemi, Fototerapi, Yenidoğan

INTRODUCTION

Phototherapy is the primary form of therapy for neonatal indirect hyperbilirubinemia (1). Although some minor side effects including ashes, loose green stools, water loss, oxidative injury, and dehydration were determined, no severe adverse reactions or long-term complications have been reported since this treatment was introduced into clinical practice in 1958 (2,3). Nevertheless, it may still possess unknown risks (4-6). As previously reported in the literature, we frequently observed that the direct bilirubin (DB) levels of some infants were elevated following phototherapy (7). Unlike indirect hyperbilirubinemia, direct hyperbilirubinemia is never normal or physiological, and early diagnosis and treatment are essential to achieving a better outcome (8,9). Therefore, it is important to differentiate phototherapy-related transient direct hyperbilirubinemia from direct hyperbilirubinemia due to other serious conditions. We retrospectively investigated our patients to determine in whom and to what extent phototherapy-related transient direct hyperbilirubinemia was observed.

METHODS

We scanned the medical records of 1301 patients who were admitted to the neonatology unit for indirect hyperbilirubinemia between October 2005 and February 2013. The digital database of our hospital was used. All infants were under the age of 15 days. Infants with a clinical condition other than indirect hyperbilirubinemia and/or a gestational age of <37 weeks were excluded from the study. Of the remaining 861 infants, 225 were subjected to the collection of blood samples to determine both the direct and total bilirubin (TB) levels before and just after the phototherapy. DB/TB>20% was used as the diagnostic criteria to define direct hyperbilirubinemia (9-12). The frequency of and possible risk factors for phototherapy-related transient direct hyperbilirubinemia were investigated.

Phototherapy was given by light-emitting diodes (LEDs) and fluorescent lamps with a peak output of 420-540 nm and an irradiance 10-40 $\mu\text{W}/\text{cm}^2/\text{nm}$. Treatment decisions to start phototherapy were made according to the recommendations of the American Academy of Pediatrics (1, 11). The treatment duration varied from 12 to 48 hours according to the clinical status of the patients. The Diazo method was used to measure DB and TB on a Roche Cobas Integra 800 analyzer (Germany).

Statistics

The data are presented as the mean (95% confidence interval) for continuous variables and as frequencies and percentage for categorical variables. Pearson's correlation coefficients were used to investigate the associations between variables. The paired sample T-test was used to compare repeated continuous variables before and after phototherapy. Repeated measures

analysis of variance (rANOVA) was used to compare repeated measurements of the bilirubin fractions according to sex, ABO and Rh incompatibility and the type of delivery. Sphericity was assessed using Mauchly's Test, and the Greenhouse-Geisser or Huynh-Feldt correction was applied whenever needed to correct the degrees of freedom. The Sidak correction was used as a post hoc test for rANOVA when there were more than two groups. A p value <0.05 was considered significant for two-tailed tests. Descriptive analysis of the data and analysis of variance were performed with SPSS 17.0 for Windows (SPSS, Chicago, IL). Before subject enrollment, the study protocol was reviewed and approved by the Hospital's Local Human Subjects Research Ethical Review Board.

RESULTS

The baseline characteristics and bilirubin fractions of the 225 infants are given in Table I, II. All patients were treated with phototherapy, and in no case was an exchange transfusion necessary. DB and DB/TB ratio were both elevated following phototherapy (Figure 1).

The frequency of phototherapy-related transient direct hyperbilirubinemia was found to be 0.9% (Table II). Although the DB levels of patients measured one to three days after phototherapy were higher than the pre-treatment values, none of the patients remained within the range indicative of direct hyperbilirubinemia.

The gestational age and the DB and DB/TB ratio at the time of admission were found to be correlated with the DB and DB/TB values following phototherapy (Table III).

The DB and DB/TB levels of infants who had ABO incompatibility increased faster than the levels of the rest of the patients; moreover, their levels returned to normal more quickly than the levels of the others (Figure 2, rANOVA $p < 0.001$ and $p < 0.001$, respectively). However, at the end of three days there was no difference. The magnitudes of the increases in DB and DB/TB were not different according to Rh incompatibility, the use of intravenous immunoglobulin, sex, birth weight or gestational age of the patients.

DISCUSSION

Current management protocols for neonatal hyperbilirubinemia in infants do not recommend the routine measurement of the DB level unless the infant is more than two weeks old. It is argued that DB measurements offer little, if any, assistance in evaluating patients with neonatal hyperbilirubinemia (7,13). Publications that reported low diagnostic importance of elevated DB suggest measuring only total bilirubin in patients with neonatal hyperbilirubinemia (7,13). Contrary to the suggestions, Mamtani et al.(14) reported that the measurement of the DB

bilirubin level can independently and additively improve the prognostication for infants with neonatal hyperbilirubinemia, especially in developing countries.

Newman et al. conducted one of the studies that recommended using only the TB levels in neonatal hyperbilirubinemia (7). In that study, 2877 infants were retrospectively investigated, and 5% of them were found to be in the range corresponding to direct hyperbilirubinemia. Most of these infants' DB levels returned to normal, and it was concluded that DB measurement is not reliable and is unnecessary in infants before they reach two weeks old. The increase in DB was mostly unexplained or attributed to false positivity of the test method used (the Jendrassik-Grof reaction). However, they also detected conjugated hyperbilirubinemia in 9 out of the 235 (4%) infants who were tested by the Ektachem method which provides a good estimate of the conjugated bilirubin levels (15).

Although the amount of direct bilirubin depends on the concentration of conjugated bilirubin, these two quantities are not the same. The accuracy of the measured concentration of DB depends on the method used. We used the diazo method in our study and it is one of the most widely used methods for measuring bilirubin levels. For methodological reasons, higher total bilirubin levels (even if it is all unconjugated) result in higher measured DB bilirubin levels with the diazo method (16). The absence of elevated DB levels in the pre-phototherapy group despite the higher TB levels following phototherapy suggests that the elevated levels were not associated with the method

Table I: Baseline characteristics of the patients.

Gestational age	38.9 ±1.3 weeks	
Birth Weight	3279 ±392 grams	
Gender (%)	Male: 53.4	Female: 46.6
Delivery (%)	Vaginal: 46.6	Caesarean: 53.4

Numbers are given as mean ± SD.

Table II: Bilirubin fractions in respect to phototherapy timing.

	Pre-phototherapy	Post-phototherapy	1-3 days after phototherapy
TB (mg/dl)	18.5 (18.1 - 19.0)	12.8 (12.5 -13.1)	12.9 (12.6 - 13.2)
DB (mg/dl)	0.62 (0.59 - 0.64)	1.01 (0.95 -1.11)	0.72 (0.68 - 0.75)
DB/TB	0.03 (0.03 - 0.04)	0.08 (0.08 -0.09)	0.06 (0.05 - 0.06)
DB/TB > %20(9 - 12)	0	2 (0.9%)	0

Numbers are given as mean (95% confidence interval) or percentage. **DB:** Direct bilirubin, **TB:** Total bilirubin.

Table III: Correlations of phototherapy-related transient direct hyperbilirubinemia.

	Gestational Age	DB_{bp}	DB/TB_{bp}
DB_{tp}	r: - 0.17 p: 0.013	r:0.30 p < 0.001	r: 0.22 p: 0.001
DB/TB_{tp}	r: - 0.19 p: 0.005	r:0.30 p < 0.001	r: 0.26 p < 0.001

DB_{tp}: Direct bilirubin level following phototherapy, **DB/TB_{tp}:** Ratio of direct bilirubin to total bilirubin following phototherapy, **DB_{bp}:** Direct bilirubin level before phototherapy, **DB/TB_{bp}:** Ratio of direct bilirubin to total bilirubin before phototherapy, **r:** Pearson correlation.

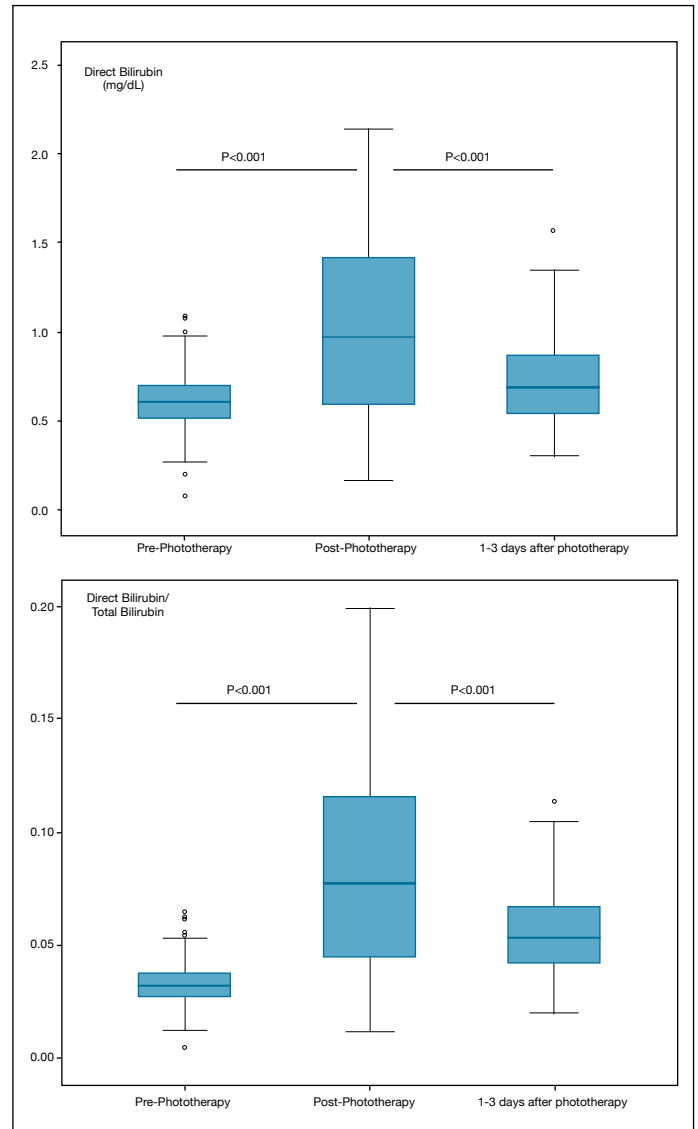


Figure 1: DB, DB/TB levels according to the effect of phototherapy. **DB:**direct bilirubin, **TB:**total bilirubin.

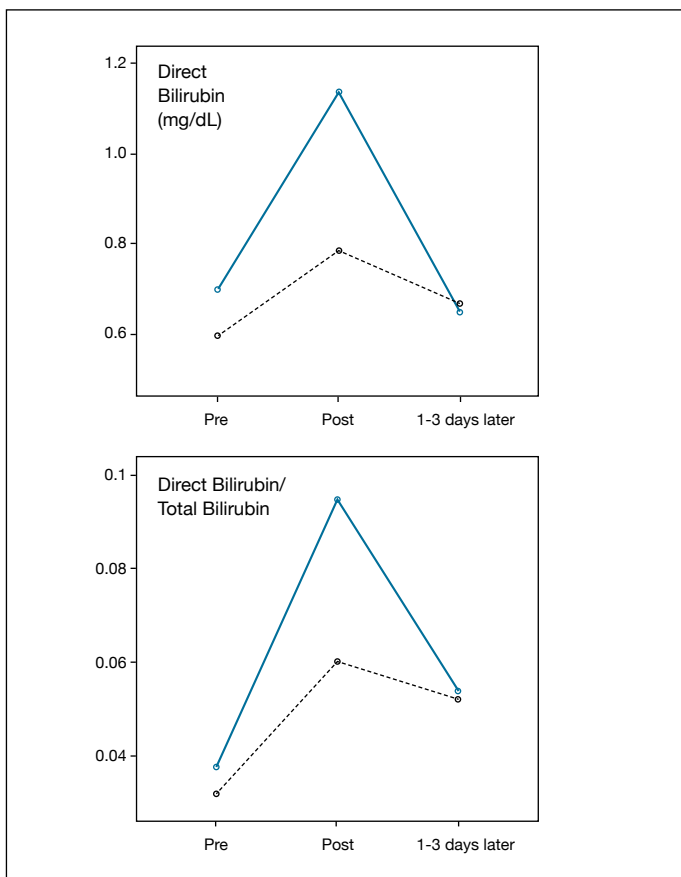


Figure 2: Change in the means of DB and DB/TB of patients with and without ABO incompatibility. ABO incompatibility, ---: the rest of the patients, **DB:** direct bilirubin, **TB:** total bilirubin, **Pre:** before phototherapy, **Post:** just after phototherapy.

used. However, the diazo method does measure bilirubin conjugates together with delta-bilirubin (17). Delta-bilirubin accounts for less than 2% of the total bilirubin in infants younger than 28 days; therefore, the detected phototherapy-related transient direct hyperbilirubinemia may be due to an increase in bilirubin conjugates or delta-bilirubin, or both (18).

Phototherapy devices other than LED may cause loss of fluid and were included in the possible explanation of bile sludge previously (19). Inspissated bile syndrome may be associated with dehydration, total parenteral nutrition and massive hemolysis (20). However, as far as we know, no ensuing study has been reported subjecting phototherapy and the inspissated bile syndrome. Conversely, babies have a better supervision on their oral intake at the hospital and are thus not prone to weight loss. In the bile, the mean concentrations of (ZZ)-bilirubin and (EZ)-cyclobilirubin increased nearly three- and ten-fold respectively, during phototherapy (21). The exact effect of these photoisomers on the bile content is not known.

Another possible explanation for the observed phototherapy-related transient direct hyperbilirubinemia is the impact of light on DB measurements. When infants' serum was irradiated with light in vitro, false increases in the DB values were detected by

the bilirubin oxidase method. However, the DB concentrations after photoirradiation remained unchanged when measured by the diazo method (22). Photoisomers of bilirubin produced during phototherapy may also react directly. Nevertheless, not much is known about this possibility (23).

In the early period after the onset of direct hyperbilirubinemia in neonates with conditions such as idiopathic neonatal hepatitis or biliary atresia, the direct reacting portion may account for only 10 - 20% of TB, and the onset of acholic stools is frequently delayed until 2 weeks of life or later. As hepatic conjugation and the uptake of bilirubin mature, IB decreases while DB increases (24-26). Therefore, a proportion of DB greater than 10% should always alert the physician. Being aware of the transient nature of phototherapy-related transient direct hyperbilirubinemia may prevent unnecessary investigations in patients incidentally found to have high levels of DB during phototherapy.

The increase in the DB levels following phototherapy seems to be reversible, and the elevated DB levels were seldom in the diagnostic zone; however, direct hyperbilirubinemia should never be considered normal or physiological. Thus, unless other studies also demonstrate a definite relationship between phototherapy and direct hyperbilirubinemia, patients in this situation should be followed up with skepticism. It is best to use the recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (cut off value of DB/TB > %20) to reduce the rate of phototherapy-related transient direct hyperbilirubinemia (9). The historically mentioned methods of DB > 2.0 mg/dL, DB > 1.5-2.0 mg/dL and/or DB/TB > 10 -20% should not be used; as the incidence of phototherapy-related direct hyperbilirubinemia would be as high as %4 and 36% respectively with these cut off values in our study (27,28).

It is also an unexpected finding that patients with ABO incompatibility had higher direct bilirubin levels during phototherapy. We could not find an explanation for this observation.

Although a significant increase in DB was observed in our patients receiving phototherapy, we do not recommend the routine measurement of DB during or after phototherapy. Both DB and the DB/TB ratio of the patients returned to normal at the end of 3 days, and there is no evidence that these transient increases have long-term side effects. Furthermore, elevated levels of DB during first two weeks of life have very low sensitivity and specificity for the management of neonatal hyperbilirubinemia (7,13).

In conclusion, the DB level and DB/TB ratio increase following phototherapy. The frequency of phototherapy-related direct hyperbilirubinemia was found to be 0.9% if the DB/TB cut-off level was set to 20%. The only identified risk factor was ABO incompatibility. Although it seems to be temporary, physicians caring for infants should be aware of this condition.

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