

## Phototherapy and serum calcium levels in full term neonates with hyperbilirubinemia

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### Abstract

**Background** Hyperbilirubinemia is one of the most common problems in newborns. Severe hyperbilirubinemia, known as kernicterus, can suppress  $O_2$  consumption and oxidative phosphorylation, as well as damage brain cells, resulting in neuronal dysfunction and encephalopathy. Phototherapy is a common therapy for neonatal hyperbilirubinemia, but may rarely lead to the adverse effect of hypocalcemia.

**Objective** To investigate serum calcium levels in full term neonates with hyperbilirubinemia, before and after phototherapy.

**Methods** This cohort study compared total serum calcium level before and after phototherapy in full term neonates with hyperbilirubinemia. Subjects were full term neonates aged 2-14 days with high total serum bilirubin levels, according to the Bhutani curve, and were treated with phototherapy at Sanglah Hospital, Denpasar, Bali, Indonesia. Paired T-test was used to compare serum calcium levels before and after phototherapy.

**Results** There were 35 subjects in this study. Paired T-test revealed that subjects' serum calcium significantly decreased after phototherapy [before: 9.47 mg/dL vs. after: 9.23 mg/dL; mean difference 0.24; (95%CI 0.03 to 0.46;  $P=0.025$ )]. None of our subjects had hypocalcemia after phototherapy.

**Conclusion** Full term neonates with hyperbilirubinemia have reduced serum calcium levels after phototherapy. [Paediatr Indones. 2021;61:8-11 ; DOI: 10.14238/pi61.1.2021.8-11 ].

**Keywords:** term neonates; hyperbilirubinemia; phototherapy; calcium

Neonatal hyperbilirubinemia, defined as total serum bilirubin level above 5 mg/dL (86  $\mu$ mol/L), is a common problem. Bilirubin is the final product of heme degradation. Although up to 60 percent of full term newborns have clinical jaundice in the first week of life, few have significant underlying disease.<sup>1</sup> Neonatal hyperbilirubinemia results from a predisposition to the production of bilirubin in newborns and their limited ability to excrete it. Infants, especially preterm infants, have higher rates of bilirubin production than adults, because their red blood cells have a higher turnover and shorter life span. In newborns, unconjugated bilirubin is not readily excreted, and the ability to conjugate bilirubin is limited.<sup>2</sup>

The main purpose in managing hyperbilirubinemia is to control bilirubin levels so that they do not reach levels that can cause kernicterus or bilirubin

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encephalopathy. Treatments to reduce newborn bilirubin levels include early breastfeeding, phototherapy, and exchange transfusion.<sup>3</sup> Phototherapy has remained the standard of care for hyperbilirubinemia in infants for four decades. Efficient phototherapy rapidly reduces the serum bilirubin concentration. The initiation time of phototherapy varies according to infant gestational age and the cause of the jaundice. Full term infants with no evidence of hemolysis should be treated according to the guidelines of the American Academy of Pediatrics.<sup>2</sup> Phototherapy is generally safe, but some side-effects include skin rash, diarrhea, increased body temperature, dehydration, DNA damage, trembling/tremors, damage to eyes, nose obstruction due to eye bandage, tanned child syndrome, and hypocalcemia.<sup>4</sup>

Hypocalcemia is one of the lesser known, but potentially adverse effects of phototherapy. Neonatal hypocalcemia is defined as total serum calcium concentration  $<7$  mg/dL (1.75 mmol/L), or ionized calcium concentration  $<4$  mg/dL (1 mmol/L) in preterm infants, and total serum calcium concentration  $<8$  mg/dL (2 mmol/L) or ionized calcium concentration of  $<4.8$  mg/dL (1.2 mmol/L) in full term infants. Ionized calcium is crucial for many biochemical processes, including blood coagulation, neuromuscular excitability, cell membrane integrity and function, as well as cellular enzymatic and secretory activity. Hypocalcemia increases cellular permeability to sodium ions and increases cell membrane excitability. It can cause serious complications like convulsions, apnea, stridor, irritability, and jitteriness.<sup>5,6</sup> Inhibition of the pineal gland due to transcranial illumination during phototherapy decreases melatonin levels. One of the functions of melatonin is to inhibit the cortisol activity. Cortisol increases calcium absorption by bones. Hence, increased cortisol levels lead to hypocalcemia. Urinary excretion of calcium is also increased following phototherapy.<sup>7</sup>

Few studies have mentioned phototherapy as a risk factor for hypocalcemia. We aimed to compare serum calcium levels in full term neonates with hyperbilirubinemia, before and after phototherapy.

## Methods

This cohort study compared serum calcium levels

before and after phototherapy in full term neonates with hyperbilirubinemia. This study was conducted in the Department of Child Health, Udayana University Faculty of Medicine, Sanglah Hospital, Denpasar, Indonesia. From January to December 2019, 35 full term neonates aged 2-14 days with high total serum bilirubin level according to the Bhutani curve<sup>3</sup> who needed phototherapy were recruited into this study. We excluded neonates who suffered from pathological jaundice, birth asphyxia, hypocalcemia before phototherapy, as well as those born to diabetic, hyperparathyroid, vitamin D or magnesium deficient mothers, or mothers who took anticonvulsant drugs. Hypocalcemia was diagnosed if the serum total calcium level was less than 8 mg/dL (2 mmol/L) for full term neonates.

After taking all aseptic precautions, approximately 2 mL blood specimens were collected from neonates before initiating phototherapy and 2 hours after discontinuation of phototherapy. Total serum bilirubin, direct bilirubin, and total serum calcium were measured in the Central Laboratory of Sanglah Hospital.

Descriptive statistical analysis was carried out. Numerical measurements with normal distribution were presented as mean (SD); numerical measurements with abnormal distribution were presented as median (min-max). Categorical measurements were presented in number (%). Quantitative data were analyzed by the paired T-test to compare total serum calcium level before and after phototherapy. The test results were considered to be significant for P values less than 0.05. Subjects' parents provided written informed consent. This study was approved by the Research Ethics Committee of Udayana University Faculty of Medicine/Sanglah Hospital, Denpasar, Indonesia.

## Results

Of 97 neonates with hyperbilirubinemia, 62 neonates were excluded because of pathological jaundice (46 neonates) or birth asphyxia (16 neonates). Characteristic data collected were age, gender, gestational age, birth weight, mode of delivery, type of nutrition, total serum bilirubin before and after phototherapy, and duration of phototherapy (Table 1). Subjects' median neonatal age was 3 (range 2 to 5)

days and 19/35 subjects were female. Subjects' median birth weight was 2,900 grams (range 2,600-3,950 grams); 18 (51.4%) subjects were delivered vaginally. Subjects' median gestational age was 38 weeks (range 37-41 weeks). Most subjects (68.6%) received breast milk. Subjects underwent phototherapy for a median duration of 3 days (range 2 -3 days). The mean total serum bilirubin levels were 14.43 (SD 1.51) mg/dL before phototherapy and 7.78 (SD 1.37) mg/dL after phototherapy.

**Table 1.** Characteristics of study subjects

Characteristics	N=35
Median age (range), days	3 (2-5)
Gender, n	
Male	16
Female	19
Median gestational age (range), weeks	38 (37-41)
Median birth weight (range), grams	2,900 (2,600-3,950)
Mode of delivery, n	
Vaginal	18
Caesarean section	17
Type of nutrition, n	
Breast milk	24
Formula milk	11
Mean total serum bilirubin before phototherapy (SD), mg/dL	14.43 (1.51)
Mean total serum bilirubin after phototherapy (SD), mg/dL	7.78 (1.37)
Median duration of phototherapy (range), days	3 (2-3)

The total mean serum calcium levels were 9.47 (SD 0.58) mg/dL before phototherapy and 9.23 (SD 0.79) mg/dL after phototherapy. Paired T-test revealed that the mean 0.24 mg/dL decrease in total mean serum calcium level from before to after phototherapy was statistically significant ( $P < 0.05$ ). As such, the total serum calcium level after phototherapy was significantly lower than before phototherapy (95%CI 0.03 to 0.46;  $P = 0.025$ ). None of the subjects had hypocalcemia after phototherapy. The analysis results are shown in **Table 2**.

## Discussion

The severity of hypocalcemia in neonates receiving phototherapy depends on many factors like duration of exposure, gestational age, and the use of double-surface or single-surface phototherapy.<sup>8</sup> In our study, 35 full term neonates with jaundice and mean total serum bilirubin level of 14.43 (SD 1.51) mg/dL were treated with phototherapy. Our study subjects underwent single-surface phototherapy for a median duration of 3 (range 2-3) days. The median gestational age was 38 (range 37-41) weeks. Mean total serum calcium levels before and after phototherapy were 9.47 (SD 0.58) mg/dL and 9.23 (SD 0.79) mg/dL, respectively (**Table 2**). The mean total serum calcium reduction after phototherapy of 0.24 mg/dL was statistically significant (95%CI 0.03 to 0.46;  $P = 0.025$ ). The use of single-surface phototherapy for a short duration in full term neonates led to the absence of hypocalcemic neonates in our study.

The hypocalcemic mechanism of phototherapy may be due to the decrease in melatonin secretion. Inhibition of the pineal gland due to transcranial illumination from phototherapy decreases melatonin levels. One of the functions of melatonin is to inhibit cortisol action. Cortisol increases calcium absorption by bone. Hence, cortisol increases may lead to hypocalcemia. Urinary excretion of calcium is also increased following phototherapy.<sup>7</sup> Our results were in agreement with a previous study which showed a significant difference between before and after phototherapy plasma calcium levels.<sup>9</sup> However, none of our subjects' calcium levels dropped into the hypocalcemia range.

The overall prevalence of hypocalcemia in neonates receiving phototherapy was reported to be 8.7% in full-term neonates.<sup>10</sup> There was no incidence of hypocalcemia after phototherapy in our study. In this study, there was a statistically significant decrease in calcium levels of 0.24 mg/dL after phototherapy. When compared with the minimum difference in total serum calcium levels that were considered significant

**Table 2.** Analysis of calcium levels before and after phototherapy

Variables	Phototherapy		Mean difference	95% CI	P value
	Before (n=35)	After (n=35)			
Mean calcium (SD), mg/dL	9.47 (0.58)	9.23 (0.79)	0.24	0.03 to 0.46	0.025

(1 mg/dL) when determining the sample size of this study, the difference in total serum calcium levels before and after phototherapy obtained in this study was much smaller and with a decrease in total serum calcium levels of 0.24 mg/dL the clinical conditions of the infants will not be different. Our study explains a statistically significant decrease in total serum calcium levels in term neonates with hyperbilirubinemia after phototherapy, but not clinically significant.

Ionized calcium was not measured in this study, and total serum calcium levels can be affected by albumin levels. Therefore, a limitation of our study was not measuring albumin. Nor did we examine cortisol levels, so we are unable to make conclusions on the mechanism of hypocalcemia due to phototherapy through increased cortisol. The reduction in calcium levels is generally greater in neonates who receive infant formula compared to breast milk, which is related to the high phosphate content of infant formula.<sup>11</sup> The calcium levels which were not compared between breastfed neonates and formula-fed neonates in our study can be considered as one of the limitations in this study because the administration of infant formula can affect the reduction in calcium level.

Further examination of ionized calcium levels is needed in order to rule out the effects of albumin and cortisol on calcium reductions before and after phototherapy. We also suggest including only breastfed neonates, not formula-fed neonates, as phosphate content in infant formula may be a confounding factor. In conclusion, there is a significant reduction in serum calcium levels after phototherapy in full term neonates with hyperbilirubinemia.

### Conflict of interest

None declared.

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