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Original Article

Rebound serum bilirubin levels after single vs. double phototherapy

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Abstract

Background Hyperbilirubinemia is the most common clinical phenomenon found in newborns. Phototherapy is the standard treatment for lowering bilirubin levels in neonates. While intensive (double) phototherapy produces a more rapid decline in serum bilirubin levels than standard (single) phototherapy, greater rebound effects may occur.

Objective To assess bilirubin levels in neonates with hyperbilirubinemia who underwent single or double phototherapy, including rebound bilirubin levels after phototherapy termination.

Methods An open, randomized, controlled trial was conducted at H. Adam Malik Hospital and Dr. Pirngadi Hospital, Medan, from August 2009 until January 2010. Subjects with indirect hyperbilirubinemia were divided into two groups. One group received single phototherapy (n = 41) and other received double phototherapy (n = 40). Measurements of total plasma bilirubin level were conducted at 12 hours and at 24 hours of phototherapy, as well as at 24 hours after phototherapy termination. Rebound bilirubin serum level was defined as an increment of about 1 – 2 mg/dL serum bilirubin after phototherapy discontinuation.

Results The decreases in serum bilirubin levels were significantly greater in the double phototherapy group for observations at 12 hours, 24 hours, and 24 hours after phototherapy termination (P = 0.0001). At the 24-hour observation after termination of phototherapy, only 1 neonate (2.7%) in the single phototherapy group compared to 4 neonates (10.8%) in the double phototherapy group had serum bilirubin level increases of 1 – 2 mg/dL. Fisher's exact test did not reveal a significant difference in rebound serum bilirubin occurrence in the two groups (P = 0.358).

Conclusion Double phototherapy shows significantly greater decrease in bilirubin level compared to single phototherapy within a same period of time. Rebound serum bilirubin levels after single and double phototherapy may occur in some patients with hyperbilirubinemia, as bilirubin production continues. However, there is no significant difference in rebound effects between single *vs.* double phototherapy. **[Paediatr Indones. 2014;54:260-5.]**

Keywords: *hyperbilirubinemia, phototherapy, rebound*

Hyperbilirubinemia is the most common clinical phenomenon found in newborns. More than 85% of newborns are readmitted to the hospital within the first week of life due to this condition.[1,2] Hyperbilirubinemia may be treated in three ways: exchange transfusion, phototherapy, and pharmacologic treatment.[3]

Phototherapy has remained the standard of care for hyperbilirubinemia treatment in infants for four decades.[4] After discontinuing phototherapy, bilirubin level often rises slightly, a phenomenon known as re-

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bound. Rebound hyperbilirubinemia is usually an elevation of no more than 1 to 2 mg per dL.[5,6] Intensive or double phototherapy produces a more rapid decline in total serum bilirubin level than standard or single phototherapy. However, a greater rebound may occur following intensive phototherapy.[7]

We aimed to compare bilirubin levels of neonates with hyperbilirubinemia who underwent single vs. double phototherapy, as well as rebound bilirubin levels in the two groups.

Methods

An open, randomized, controlled trial was conducted in H. Adam Malik and Dr. Pirngadi Hospitals, Medan, Indonesia, from August 2009 until January 2010. For 81 neonates with indirect hyperbilirubinemia, simple randomization using sealed and uniform envelopes was carried out to divide subjects into two groups: single phototherapy (n = 41) or double phototherapy (n = 40). The need for phototherapy was determined using the American Academy of Pediatrics guidelines for management of jaundice in healthy term newborns.[2,9] Neonates who had serum bilirubin levels close to the exchange transfusion limit, increased direct bilirubin, hemolytic disease, or congenital anomalies were excluded from the study. Total bilirubin levels were measured at 12 hours and 24 hours of phototherapy, as well as at 24 hours after phototherapy termination. This study was approved by the Medical Ethics Committee at the University of Sumatera Utara.

Clinically jaundiced subjects underwent routine blood tests for bilirubin, blood cultures, Coombs test, and albumin, from 5 cc blood specimens taken from a peripheral vein. Subjects received phototherapy treatment with units manufactured by Tessna, USA, with five compact blue fluorescent lamps (Toshiba 20WT52) of irradiance 8 to 10 $\mu W/cm^2$/nm and wavelength 452 to 475 nm. For the single phototherapy group the distance between the phototherapy unit and the baby bassinet was 40 cm. For the double phototherapy group, a phototherapy unit was placed 40 cm above the bassinet and another unit placed 10 cm below bassinet.

Examination of serum bilirubin levels was performed using an automatic Cobas 6000 and Integra 400 analyzer manufactured in 2007. During the period of the study, light intensity was measured using a radiometer (*Dale 40*).

During phototherapy, subjects used eye protection and were monitored for dehydration. Both groups received 10% of their total fluid needs either orally or intravenously. Phototherapy was stopped when normal bilirubin levels were reached, in accordance with the American Academy of Pediatrics criteria, or if phototherapy side effects were observed, such as dehydration, hyperthermia, lethargy, or irritability.[2, 9]

We analyzed data using *SPSS version 14.0* with 95% confidence intervals (95% CI). The significance level was accepted as $P < 0.05$. Differences in serum bilirubin levels before phototherapy, at 12 hours, and at 24 hours of phototherapy, as well as at 24 hours after phototherapy termination, were analyzed using independent T-test. Differences in rebound effects in the two groups after phototherapy were analyzed using Fisher's exact test.

Results

During the study period there were 83 neonates with hyperbilirubinemia, but 2 neonates were excluded (one with multiple congenital anomalies and one with direct hyperbilirubinemia). Therefore, 81 neonates with hyperbilirubinemia were eligible for the study. Neonates were randomized into two groups to receive either single phototherapy (n = 41) or double phototherapy (n = 40). (**Figure 1**) Baseline characteristics of subjects were similar as shown in **Table 1**.

We examined subjects' bilirubin levels before phototherapy, at 12 hours and 24 hours of phototherapy, and 24 hours after phototherapy was terminated.

Mean initial serum bilirubin levels were not significantly different between the single and double phototherapy groups. At 12 and 24 hours of phototherapy, as well as 24 hours after phototherapy termination, mean bilirubin levels were significantly lower in the double phototherapy group than in the single phototherapy group (P=0.0001) (**Table 2**).

Table 3 shows that the mean decreases in serum bilirubin levels were greater in the double phototherapy group at the 12 hour and 24 hour observations, as well as at 24 hours after phototherapy termination (P = 0.0001).

Serum bilirubin monitoring at 24 hours after

phototherapy was stopped revealed that one neonate (2.7%) from the single phototherapy group compared to 4 neonates (10.8%) from the double phototherapy group experienced rebound serum bilirubin levels (**Table 4**). The difference was not statistically significant (P=0.358).

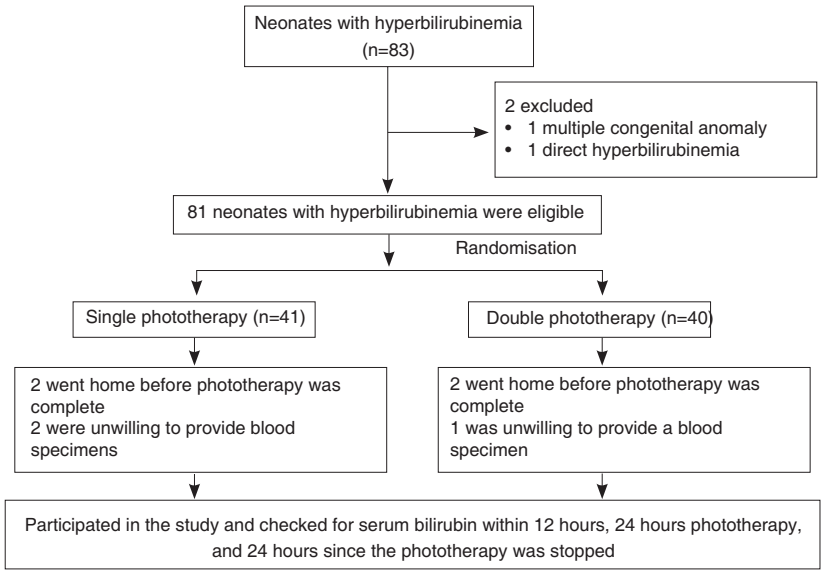

Figure 1. Study profile

Table 1. Baseline characteristics of subjects

Characteristics	Single phototherapy (n=41)	Double phototherapy (n=40)
Gender, n (%)		
Male	22 (53.7)	22 (55)
Female	19 (46.3)	18 (45)
Mean age at phototherapy (SD), days	4.6 (1.38)	4.5 (1.22)
Gestational age, n (%)		
36-38 weeks	18 (43.9)	18 (45)
38-40 weeks	23 (56.1)	22 (55)
Mean weight (SD), grams	2720.7 (228.30)	2657.7 (193.38)
Mean temperature (SD), ºC	36.7 (0.28)	36.8 (0.28)
Mean serum albumin level (SD), g/dL	2.7 (0.34)	2.6 (0.29)
Mean hematocrit (SD), %	36.1 (4.39)	35. (33.3)
Mean hemoglobin (SD), g/dL	(1.65)	14.5 (2.03)
Mean phototherapy irradiance (SD), μw/cm^2/nm		
Initial	8.6 (4.88)	29.2 (0.91)
12 hours	8.2 (1.15)	29.1 (0.66)
24 hours	8.1 (1.09)	29.3 (0.82)

Table 2. Distribution of serum bilirubin levels in the single vs. double phototherapy groups

Variables	Single phototherapy	Double phototherapy	95% CI of differences	P value
Mean initial bilirubin level (SD), mg/dL	17.8 (1.80)	17.4 (1.44)	-0.294 to 1.149	0.241
Mean bilirubin level at 12 hours of phototherapy (SD), mg/dL	17.5 (1.86)	11.4 (1.87)	5.261 to 6.912	0.0001
Mean bilirubin level at 24 hours of phototherapy (SD), mg/dL	15.6 (1.77)	8.2 (2.32)	6.509 to 8.383	0.0001
Mean bilirubin level at 24 hours after phototherapy was stopped (SD), mg/dL	11.8 (2.12)	4.6 (4.09)	5.696 to 8.715	0.0001

Table 3. Distribution of the decrease in serum bilirubin levels during phototherapy and 24 hours after phototherapy was stopped

Variables	Single phototherapy	Double phototherapy	95 % CI of differences	P value
Mean initial bilirubin level (SD), mg/dL	17.8 (1.80)	17.4 (1.44)	-0.294 to 1.149	0.241
Mean decrease in serum bilirubin levels at 12 hours of phototherapy (SD), mg/dL	0.3 (0.58)	6.0 (1.40)	5.177 to 6.131	0.0001
Mean decrease in serum bilirubin levels at 24 hours of phototherapy (SD), mg/dL	2.2 (1.27)	9.3 (2.10)	6.256 to 7.482	0.0001
Mean decrease in serum bilirubin levels 24 hours after phototherapy was stopped (SD), mg/dL	5.9 (1.87)	12.7 (4.14)	5.404 to 8.380	0.0001

Table 4. Distribution of subjects who experienced rebound serum bilirubin at 24 hours after phototherapy termination

Variables	Single phototherapy	Double phototherapy	P value
Rebound, n (%)	1 (2.4)	4 (10)	0.358
No rebound, n (%)	40 (97.6)	36 (90)	

Discussion

The average age of subjects in our study was 4 days. This young age is related to the incidence of physiologic jaundice as a frequent problem, occurring in 60 – 70% of term newborns and 80% of infants born prematurely, during their first week of life.[8,9]

The goal of phototherapy is to lower the concentration of circulating bilirubin or keep it from increasing.[6,10] Between the single and double phototherapy groups, there were significant decreases in serum bilirubin levels at the 12-hour and 24-hour phototherapy time points, as well as at the 24-hour post-phototherapy point.

The effectiveness of phototherapy depends on the intensity of the light source (irradiance). The higher the intensity, the faster the decline in serum bilirubin level.[5,11] Spectral irradiance is quantified as $\mu W/cm^2/nm$. It can be measured with a spectral radiometer sensitive to the effective wavelength of light.[5] Intensity of light (irradiance) depends on the wavelength, light source design, distance and exposed body surface area.[3,5,12] The most effective lights are those with wavelength predominantly in the blue-green spectrum (425 to 490 nm). At this wavelength range, light penetrates the skin well causing bilirubin to undergo photochemical reactions to form excretable isomers and breakdown products.[3,5,6,12] Light intensity can be enhanced by using intensive or double phototherapy. This can be achieved by placing light sources below and above the neonate.[5,6]

In our study, the single phototherapy group used a blue photolight (Toshiba 20WT52) with spectral irradiance of 8.05 ± 1.09 μW/cm2/nm to 8.63 ± 4.88 $\mu W/cm^2/nm$, at the distance of 40 cm above the neonate's bassinet. In the double phototherapy group, photolight units were placed 40 cm above and 10 cm below the neonate's bassinet. The spectral irradiance was 29.15 ± 0.66 $\mu W/cm^2/nm$ to 29.30 ± 0.82 $\mu W/cm^2/nm$. The decreases in serum bilirubin levels were significantly greater in the double phototherapy group for observations at 12 hours, 24 hours, and 24 hours after phototherapy termination (P = 0.0001).

A study in Turkey reported that double phototherapy provided more rapid and effective bilirubin reduction than single phototherapy, due to higher spectral irradiance and larger body surface area exposed to phototherapy.[13] Similarly, a Bangkok study found that double phototherapy was significantly more effective in reducing serum bilirubin levels than single phototherapy in term, jaundiced infants after 24 and 48 hours of treatment.[14] In contrast, Brazilian research found that double phototherapy was not more effective than single phototherapy in the treatment of hyperbilirubinemia in term newborns.[15]

Neonates treated for high bilirubin levels may suffer from dehydration and require additional fluid intake.[8] Increased body temperature, the environment, insensible water loss, increased respiratory

rate and blood flow to the skin are determined by the maturity of the neonate, adequate calorie intake, temperature adjustment of the photolight unit, the distance between the neonate and photolight, and the incubator. Increased peripheral blood flow can increase fluid loss, requiring the administration of intravenous fluids.[8,16] Skin changes, such as rash, darker skin color and burns can be seen after overexposure to fluorescent light.[17]

Body temperature and fluid administration were strictly monitored in our subjects. Fluid intake was given every 2 hours, and was increased by 10 – 20% of the total fluid requirement. In breastfed neonates, phototherapy was withheld during breastfeeding.[19,20] During this study, the side effect of hyperthermia (T>37.5ºC) was found in 3 neonates (0.07%) and 5 neonates (0.1%) in the single and double phototherapy groups, respectively.

Rebound hyperbilirubinemia is usually an elevation of no more than 1 to 2 mg per dL, after phototherapy is discontinued.[5,7] Neonates at increased risk of a clinically significant rebound are those born at less than 37 weeks gestation, those with hemolytic disease, and those treated with phototherapy during the birth hospitalization.[6] Serum bilirubin measurements obtained 24 hours after discontinuation of phototherapy will detect rebound hyperbilirubinemia.[5]

A prospective, clinical study in Israel reported that post-phototherapy neonatal bilirubin rebound to clinically significant levels may occur, especially in neonates with prematurity, positive direct Coombs test, and those treated ≤ 72 hours.[21] A retrospective study in Houston found there were no statistically significant differences among infants in the smaller weight categories, regardless of Coombs test results. Infants completing phototherapy for hyperbilirubinemia who are otherwise healthy do not require follow up solely to check for rebound bilirubin levels.[22] Another retrospective study in Saudi Arabia found that the rebound of serum bilirubin level after termination of phototherapy in otherwise healthy, term infants was minimal, thus measurement of serum bilirubin level is not required after phototherapy termination, as it adds unnecessary expense, prolongs hospitalization, or both.[23]

Intensive phototherapy produces a more rapid decline in total serum bilirubin level than standard phototherapy, however, a greater rebound effect may occur.[7] Intensive phototherapy rapidly decreases serum bilirubin to below the threshold for treatment. However, underlying alterations in bilirubin production and excretion may persist, causing bilirubin rebound after stopping phototherapy.[24]

An Indian study found that of 232 neonates, 17 (7.3%) neonates developed serum bilirubin rebound, at a level of 2.3 mg/dL. Risk factors for rebound serum bilirubin included birth at < 35 weeks gestation, birthweight < 2000 grams, and onset of jaundice at < 60 hours of age.[24] In our study, one neonate (2.7%) in the single phototherapy group had rebound serum bilirubin at 24 hours after therapy termination. The gestational age in both groups was 36 – 38 weeks. Fisher's exact test revealed no significant difference in rebound bilirubin serum cases between groups (P = 0.358).

The American Academy of Pediatrics recommended that infants need not be hospitalized to measure rebound bilirubin levels following the discontinuation of phototherapy.[7] Hospital discharge does not need to be delayed for observation of rebound in such cases.[10,25] However, in the presence of hemolytic disease or in sick or low birth weight infants, such reassurance may not be warranted. Because hemolysis or other processes responsible for increased bilirubin production may continue, the rebound in these cases depends not only on the effectiveness of phototherapy, but also on the bilirubin production.[10]

In conclusion, double phototherapy shows significantly greater decrease in bilirubin level compared to single phototherapy. Rebound effect may occur after the termination of both treatments. However, there is no significant difference of rebound effect between double and single phototherapy.

References

1. Wong RJ, Stevenson DK, Ahlfors CE, Vreman HJ. Neonatal jaundice: bilirubin physiology and clinical chemistry. NeoReviews. 2007;8:e58-67.
2. Sukadi A. Hiperbilirubinemia. In: Kosim MS, Yunanto A, Dewi R, Sarosa GI, Usman A, editors. Buku ajar neonatologi. 1st ed. Jakarta: Badan Penerbit IDAI; 2008. p.147-69.
3. Maisels M. Neonatal hyperbilirubinemia. In: Polin RA, Yodes MC, editors. Workbook in practical neonatology. 4th ed. Philadelphia: Saunders; 2007. p.53-70.

4. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. N Engl J Med. 2001;344:581-90.
5. Stokowsky LA. Fundamentals of phototherapy for neonatal jaundice. Adv Neonatal Care. 2006;6:302-12.
6. Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. N Engl J Med. 2008; 358:920-8.
7. Maisels MJ, Kring E. Rebound in serum bilirubin level following intensive phototheraphy. Arch Pediatr Adolesc Med. 2002;156:669-72.
8. Gomella TL. Hyperbilirubinemia indirect. In: Gomella TL, Cunningham MD, Eyal FG, editors. Neonatology: management, procedures, on-call problems, disease, and drugs. 5th ed. New York: McGraw-Hill; 2004. p.247-50.
9. Madan A, Macmahon JR, Stevenson DK. Neonatal hyperbilirubinemia. In: Taeusch HW, Ballard RA, Gleason CA, editors. Avery's disease of the newborn. 8th ed. Philadelphia: Elsevier Saunders; 2005. p.1226-53.
10. Suradi R, Situmeang EH, Tambunan T. The association of neonatal jaundice and breast-feeding. Paediatr Indones. 2001;41:69-75.
11. Djokomuljanto S, Quah BS, Surini Y, Noraida R, Ismail NZN, Hansen TW, *et al*. Efficacy of phototherapy for neonatal jaundice is increased by the use of low-cost white reflecting curtains. Arch Dis Child Fetal Neonatal. 2006;91:439-42.
12. Maisels MJ. Phototherapy-traditional and nontraditional. J Perinatol. 2001;21:93-7.
13. Sarici SU, Alpay F, Unay B, Ozcan O, Gokcay E. Double versus single phototherapy in term newborns with significant hyperbilirubinemia. J Trop Pediatr. 2000;46:36-9.
14. Boonyarittipong P, Kriangburapa W, Booranavanich K. Effectiveness of double-surface intensive phototherapy versus single-surface intensive phototherapy for neonatal hyperbilirubinemia. J Med Assoc Thai. 2008;91:50-5.
15. Silva I, Luco M, Tapia JL, Perez ME, Salinas JA, Flores J, Villaroel L. Single vs. double phototherapy in the treatment of full-term newborns with nonhemolytic hyperbilirubinemia. J Pediatr (Rio J). 2009;85:455-8.
16. Kang JH, Shankaran S. Double phototherapy with high irradiance compared with single phototherapy in neonates with hyperbilirubinemia. Am J Perinat. 1995;12:178-80.
17. Grunhagen DJ, De Boer MG, de Beaufort AJ, Walther FJ. Transepidermal water loss during halogen spotlight phototherapy in preterm infants. Pediatr Res. 2002;51:402-5.
18. Martin CR, Cloherty JP. Neonatal hyperbilirubinemia. In: Cloherty JP, Eichenwald EC, Stark AR, editors. Manual of neonatal care. 5th ed. Philadelphia: Lippincott, Williams & Wilkins; 2004. p. 183-221.
19. Bagchi A. Phototherapy. In: MacDonald MG, Ramasethu J, editors. Procedures in neonatology. 3rd ed. Philadelphia: Lippincott, William & Wilkins; 2002. p. 373-8.
20. Hansen TW. Phototherapy for neonatal jaundice-therapeutic effects on more than one level? Semin Perinatol. 2010;34: 231-4.
21. Kaplan M, Kaplan E, Hammerman C, Algur N, Bromiker R, Schimmel MS, *et al*. Post-phototherapy neonatal bilirubin rebound: a potential cause of significant hyperbilirubinaemia. Arch Dis Child. 2006;91:31-4.
22. Yetman RJ, Parks DK, Huseby V, Mistry K, Garcia J. Rebound bilirubin levels in infants receiving phototherapy. J Pediatr. 1998;133:705-7.
23. Al-Saedi SA. Rebound hyperbilirubinemia in term infants after phototherapy. Saudi Med J. 2002;23:1394-7.
24. Bansal A, Jain S, Parmar VR, Chawla D. Bilirubin rebound after intensive phototherapy for neonatal jaundice. Indian Pediatr. 2010;47:607-9.
25. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297-316.