Comparison of the Effectiveness Between the Adapted-Double Phototherapy *Versus* Conventional-Single Phototherapy

PRACHA NUNTNARUMIT, M.D.*,
CHONLATHIT NAKA, M.D.*

Abstract

Background : Jaundice is very common in neonates during the first few days of life. Severe hyperbilirubinemia is potentially neurotoxic, resulting in bilirubin encephalopathy. Phototherapy has been used widespread and proven to be effective in lowering serum bilirubin. The efficacy of phototherapy depends on the type of light-source, the intensity of light and the area of skin exposed. Double phototherapy with a fiber-optic blanket has been reported to be more effective in reducing bilirubin than conventional phototherapy. However, a fiber-optic blanket or bili-bed is very expensive, thus the authors designed the adapted-double phototherapy by using ordinary fluorescent lamps that are much cheaper and more easily available.

Objective : To compare the efficacy and safety of adapted-double phototherapy (DP) using daylight fluorescent lamps to conventional phototherapy (CP) in healthy term infants with hyperbilirubinemia.

Design : Prospective randomized controlled trial study.

Method : Term infants who met phototherapy criteria were randomized into two groups of phototherapy; the adapted DP placing daylight fluorescent lamps 38 cm above and 32 cm below the crib to produce 9-10 $\mu w/cm^2/nm$ (n=24) *versus* CP of similar irradiance (n=27).

Result : There were no significant differences between the two groups with respect to birth weight, gestational age, hematocrit at enrollment and cause of hyperbilirubinemia. Infants in the DP group had higher bilirubin levels and were slightly older at the time of enrollment than those in the CP group. The bilirubin reduction rate after therapy was significantly greater in the DP compared to CP; 0.22 ± 0.12 mg/dl/h *vs* 0.14 ± 0.1 mg/dl/h on day 1 of therapy (p=0.02) and 0.16 ± 0.11 mg/dl/h *vs* 0.1 ± 0.05 mg/dl/h on day 2 (p=0.06). Duration of phototherapy was shorter in DP; 34.9 ± 12.6 h *vs* 43.7 ± 17.5 h in CP group (p=0.039). No differences in side effects were found between two groups.

Conclusion : The adapted-DP using daylight fluorescent lamps in this study has proven to be safe and more effective in reducing bilirubin than CP. It could be an alternative model for intensified phototherapy as it produces a reasonable cost-effectiveness and is easy to apply.

Key word : Double Phototherapy, Neonatal Jaundice

NUNTNARUMIT P & NAKA C
J Med Assoc Thai 2002; 85 (Suppl 4): S1159-S1166

* Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Hyperbilirubinemia or jaundice is a common condition in neonates, approximately 60 per cent in term newborn infants or 80 per cent in preterm newborn infants[1,2]. Severe hyperbilirubinemia is potentially neurotoxic, resulting in kernicterus (bilirubin encephalopathy). The treatments, for pathological jaundice basically including phototherapy, exchange transfusion, and pharmacological agents[3, 4], aim to prevent increasing bilirubin to a dangerous level. Phototherapy is a widespread method for reducing bilirubin. The mechanisms, by which light interacts with bilirubin and enhances its elimination through renal and biliary tract excretion, are photoxidization, configuration isomerization, and structural isomerization[5]. The factors determining the efficacy of phototherapy are the types of light, the intensity of light (irradiance), and the body surface area[6-10]. The effect of light intensity in reducing bilirubin is a dose-response relationship[8,9]. Its effect is noted at the light intensity (irradiance) of 4 $\mu w/cm^2/nm$[11] with a maximum response at a level of 40 $\mu w/cm^2/nm$[7]. The area exposed to the light is another important factor; Garg AK et al found that a double surface phototherapy was more effective than a conventional phototherapy in reducing bilirubin[12]. Double phototherapy using a combination of a fiber optic blanket and conventional phototherapy has reported its efficacy in preterm infants[13,14] but not in term infants. Since a biliblanket is costly and not widely available in Thailand and there are very limited studies of using double phototharapy, the authors conducted a study of using adapted-double phototherapy, which was cheap and easy to assemble, to determine the efficacy and safety compared to conventional-single phototherapy.

METHOD

A prospective randomized controlled trial was conducted in the nursery, Maharat Nakhon Ratchasima Hospital, from July 2001 to April 2002. Infants who met the inclusion criteria were term newborn infants with birth weight equal or more than 2,500 g and gestational age more than 37 weeks and required phototherapy as the American Academy of Pediatrics guideline for management of term infants with jaundice; starting phototherapy if bilirubin $\geq$ 12 mg/dl at 24-48 hours post-natal age, bilirubin $\geq$ 15 mg/dl at 49-72 hours post-natal age and if bilirubin $\geq$ 17 mg/dl at $\geq$ 72 hours post-natal age[2]. Informed consent was obtained from a parent. Infants who were on ventilator support or in an incubator, or had been on phototherapy before enrollment, or had direct hyperbilirubinemia, were excluded. Hemolytic jaundice was defined as jaundice associated with the following conditions: ABO, or Rh, or minor blood group incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency with an acute hemolysis, hereditary red blood cell membrane defects, jaundice within 24 hours of life or rapid rising of bilirubin more than 0.5 mg/dl/h with a high reticulocyte count (more than 5% at < 48 hours of age)[15]. Phototherapy was discontinued when bilirubin level of < 12 mg/dl at < 96 hours post-natal age or when bilirubin level of < 15 mg/dl at > 96 hours post-natal age was reached.

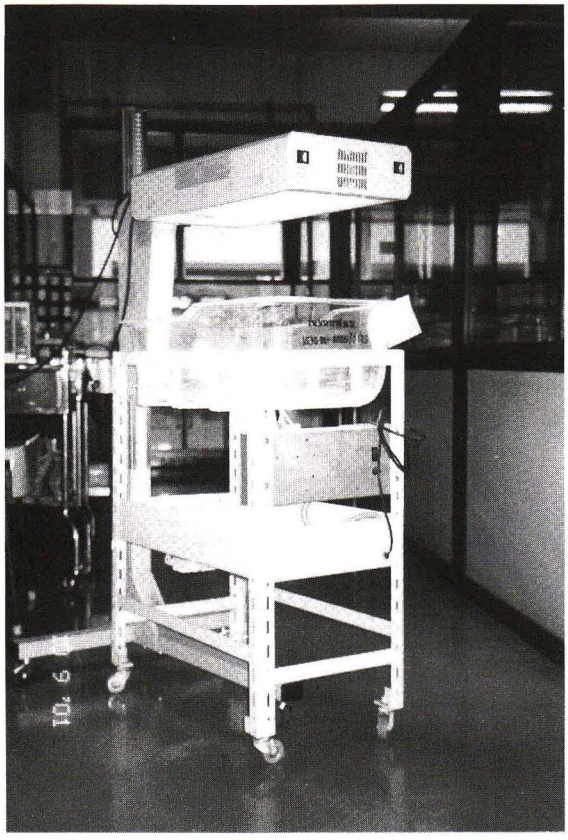

Fig. 1. Adapted-double phototherapy; the upper light source is light from conventional phototherapy, the lower light source is a set of eight 20 w-daylight fluorescent lamps, which is adjustable below the crib according to the desired irradiance. A ventilated fan is placed between the crib and the light source in order to ventilate and prevent overheating.

The infants who met the criteria were randomized into two groups; the conventional (single) phototherapy (CP) group and the adapted-double phototherapy (DP) group. The CP was comprised of 3 daylights and 2 blue lights. The adapted-DP was comprised of 2 light sources, the upper and the lower light sources (Fig. 1). The upper light source was from a CP and the lower light source below the crib consisted of 8 lamps of 20-watt daylight fluorescents. The lower light source could be adjusted away from the crib accordingly to obtain the targeted irradiance. The target of light intensity (irradiance) was set at 9-10 $\mu w/cm^2/nm$ measured by the photoradiometer PR III® (Air shields Inc., Pennsylvania, USA). The required distance from an infant to the light source in order to achieve the target irradiance was 38 cm above and 32 cm below the crib. A small fan was placed in between the crib and the lower light source to ventilate and prevent overheating to the infant. The light intensity was measured to confirm the targeted intensity before starting phototherapy on every infant. Pre-phototherapy laboratory tests were obtained in all infants including hematocrit, microbilirubin, blood group, complete blood count, red blood cell morphology, glucose-6-phosphate dehydrogenase level, direct Coombs and indirect Coombs test as well as maternal blood group. The microbilirubin was measured by the bilirubin meter Bil Read® (Optima Inc., Tokyo, Japan). The hematocrit and microbilirubin were followed every 12 hours until discontinuation of the therapy and repeated again 24 hours later. The body weight change, temperature and frequency of stooling and voiding were recorded. Routine nursing cares was similarly applied to all infants. Primary outcome

measurements included the rate of bilirubin reduction, duration of phototherapy and side effects related to the phototherapy. Secondary outcome measurement was the rate of exchange transfusion in each group.

Statistical analysis

To detect a difference in bilirubin reduction of 2 mg/dl a day, at least 22 infants in each group were required, assuming a mean bilirubin of 17 mg/dl at entry with a power of 90 per cent and a p-value of less than 0.05. Data on continuous variables were compared by the Student's *t*-test and data on categorical variables were compared by the Chi-square and Fisher's exact tests.

RESULTS

Fifty-one infants, 27 in the CP group and 24 in the DP group, were enrolled. The mean birth weight was 3102 ± 333 g and the mean gestational age was 38.8 ± 1.3 weeks. No differences were found between the groups such as birth weight, gestational age, gender and hematocrit at entry, but infants in the DP group had higher bilirubin levels and were older than infants in the CP group (Table 1).

The cause could not be identified in most of the infants (75% in the DP group and 78% in the CP group) (Table 2). The proportion of infants with hemolytic jaundice were 20.8 per cent in the DP group and 14.8 per cent in the CP group. Causes of hemolytic jaundice were ABO incompatibility, Rh incompatibility, minor blood group incompatibility, and G6PD deficiency.

Fig. 2 shows the bilirubin reduction rate. During the first 24 hours of therapy, the adapted-DP reduced bilirubin faster than that of the CP; 0.22 ± 0.12 mg/dl/h *vs* 0.14 ± 0.1 mg/dl/h, p-value = 0.02. The adapted-DP also showed a tendency to reduce bilirubin faster in day 2 of treatment (0.61 ± 0.11 mg/dl/h *vs* 0.1 ± 0.05 mg/dl/h, p-value = 0.06). Regarding the duration of phototherapy, there was a significantly shorter duration of therapy in the DP group; 34.9 ± 12.6 hours *vs* 43.7 ± 17.5 hours in CP group, p-value = 0.039.

Table 3 shows the side effects related to the phototherapy. There were no significant differences between the groups with respect to number of infants with fever, frequency of stooling and percentage of weight reduction. None of the infants in either group

Table 1. Characteristics of the study population.

Characteristics	Double phototherapy (n = 24)	Conventional phototherapy (n = 27)	P-value
Sex (M : F)	15 : 9	19 : 8	0.52
Birth weight (g)	3,077 ± 25	3,128 ± 391	0.59
Gestational age (wk)	38.7 ± 1.3	38.8 ± 1.3	0.76
Age at entry (h)	83.9 ± 27.7	66.3 ± 24.8	0.03
Hematocrit at entry (%)	49.6 ± 6.5	49.9 ± 7.3	0.8
Microbilirubin at entry (mg/dl)	19.5 ± 2.6	17.7 ± 2.6	0.013

Table 2. Causes of hyperbilirubinemia in the study population.

Causes of hyperbilirubinemia	Double phototherapy		Conventional phototherapy	
	n	%	n	%
ABO incompatibility	3	12.5	2	7.4
Rh incompatibility	-		1	3.7
Minor blood group incompatibility	-		1	3.7
G6PD deficiency (hemolysis)	2	8.3	-	
Cephalhematoma	1	4.2	-	
Polycythemia	-		2	7.4
Unidentified	18	75	21	77.8
Total	24	100	27	100

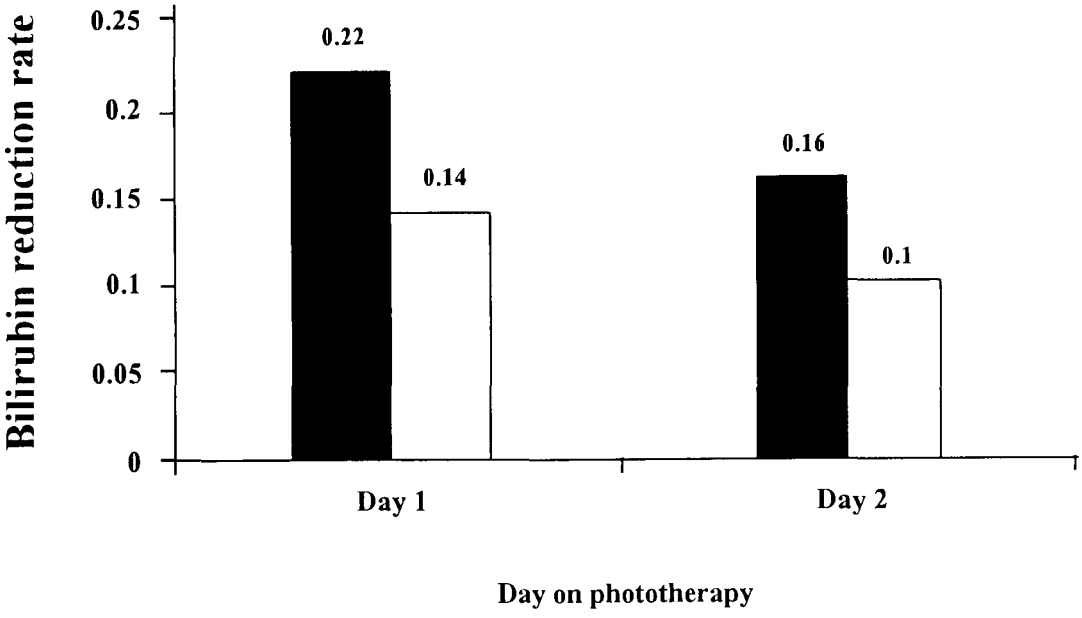

Fig. 2. Comparison of the bilirubin reduction rate between the two types of therapy. There was a significant reduction in the double phototherapy group on day 1 (p=0.02) and a trend to reduce faster on day 2 (p=0.06). ■ represents double phototherapy and ▯ represents conventional phototherapy.

Table 3. Comparison of mean ± SD of side effects related to phototherapy between the two groups.

Side effects	Double phototherapy (n = 24)	Conventional phototherapy (n = 27)	P-value
Weight reduction (%/day)	1.2 ± 0.8	1.7 ± 1.3	0.25
Frequency of stooling (times/day)	2.2 ± 1.4	2.8 ± 1.7	0.10
Fever > 38.0°C, n (%)	3 (12.5)	2 (7.4)	0.65

required exchange transfusion, one infant in the CP group had rebound jaundice and required an additional course of phototherapy.

DISCUSSION

The adapted-DP in this study showed a significant reduction in bilirubin level and duration of therapy compared to the CP in term newborn infants with hyperbilirubinemia. These results support the findings of Garg et al[12] who used high intensity double phototherapy on fluid bed with light intensity of 20-30 μw/cm^2/nm, resulting in a bilirubin reduction rate of 0.312 ± 0.91 mg/dl/h. However, the rate of bilirubin reduction in the present study was slightly lower than that of Grag's study, probably due to lower light intensity. To increase the light intensity in the present study, the light source must be placed closer to the infant, which may increase side effects related to phototherapy. The light intensity of approximately 10 μw/cm^2/nm used in the present study is generally accepted to be effective in reducing bilirubin level[15,16], more light intensity could be achieved by adjusting the distance of light source or placing more fluorescent lamps.

With appropriate and intensive phototherapy, using double surface phototherapy should theoreti-

cally be more effective in reducng bilirubin level and the chance of exchange transfusion[4]. At present, exchange transfusions are performed mostly for severe hyperbilirubinemia. Current retrospective studies have reported a complication rate of 5.2 per cent and a mortality of 0.4-3.2 per cent[17-20], therefore the best way to prevent complications associated with exchange transfusion is to reduce its use by means of effective phototherapy such as intensified double surface phototherapy. In the present study, none of the infants required exchange transfusion, but one infant in the CP group required a second course of therapy due to rebound hyberbilirubinemia 24 hours after discontinuation of treatment.

There were no differences in side effects related to phototherapy between the groups including fever, weight loss, or diarrhea; also there were no complaints from the nurses who were taking care of these infants during the adapted-DP. Overheating of the infants was prevented by placing a ventilated fan below the crib and allowing enough space around the crib. The adapted-DP used in the present study is easy to assemble and much cheaper than a manufactured bili-bed for intensified DP. The present findings also show its efficacy in reducing bilirubin level and shortening duration of the therapy. A larger study is warranted to determine the efficacy especially in hemolytic diseases.

(Received for publication on September 16, 2002)

REFERENCES

1. Behrman RE. Jaundice and hyperbilirubinemia in the newborn. In: Behrman RE, ed. Nelson textbook of pediatricts. 15th ed. Philadelphia: WB Saunders Co, 1996: 493-9.
2. Provisional Committee for Quaity Improvement and Subcommittee on Hyperbilirubinemia : Practice parameter : Management of hyperbilirubinemia in the healthy term newborn. Pediatrics 1994; 94: 558-65.
3. Valaes T, Petmezaki S, Henschke C, Drummond GS, Kappas A. Control of jaundice in preterm newborn by an inhibitor of bilirubin production: Studies with tin-mesoporphyrin. Pediatics 1994; 93: 1-11.
4. Brown AK, Kim MH, WU PY, Bryla DA. Efficacy of phototherapy in prevention and management of neonatal hyperbilirubinemia. Pediatrics 1985; 75 (Suppl): 393-400.
5. McDonagh AF, Lightner DA. Like a shrivelled blood orange: Bilirubin, jaundice and phototherapy. Pediatrics 1985; 75: 443-55.
6. Ennever JF. Blue light, green light, white light, more light : Treatment of neonatal jaundice. Clin Perinatol 1990; 17: 467.
7. Tan KL. The pattern of bilirubin response to phototherapy for neonatal hyperbilirubinemia. Pediatr Res 1982; 16: 670-4.
8. Modi N, KEAY AJ. Phototherapy for neonatal hyperbilirubinemia : The importance of dose. Arch Dis Child 1983; 58: 406-9.
9. Tan KL. The nature of the dose-response relationship of phototherapy for neonatal hyperbilirubinemia. J Pediatr 1977; 90: 448-52.
10. Tan KL. Comparison of the effectiveness of single direction and double-direction phototherapy for neonatal jaundice. Pediatrics 1975; 56: 550-3.
11. Bonta BW, Warshan JB. The importance of radiant flux in the treatment of hyperbilirubinemia : Failure of overhead phototherapy units in intensive care units. Pediatrics 1976; 57: 502-5.
12. Garg AK, Prasad RS, Hifzi I Al. A controlled trial of high-intensity double-surface photothrapy on a fluid bed *versus* conventional phototherapy in neonatal jaundice. Pediatrics 1995; 95: 914-6.
13. Holtrop PC, Ruedisueli K, Maisels MJ. Double *versus* single phototherapy in low birth weight newborns. Pediatrics 1992; 90: 674-7.
14. Tan KL. Efficacy of bidirectional fiber-optic phototherapy for neonatal hyperbilirubinemia. Pediatrics 1997; 99: E13.
15. Harold E. Bland. Jaundice in the healthy term neonate: When is treatment indicated? Curr Probl Pediatr 1996; 26: 355-63.
16. Craig J. Adverse events associated with exchange transfusion in healthy and ill newborns. Pediatrics 1997; 99: E7.
17. Keenan WJ, Novak KK, Sutherland SM, Bryla DA, Fetterly KL. Morbidity and mortality associated with exchange transfusion. Pediatrics 1985; 75 (Suppl): 422-6.
18. Hovi L, Siimes MA. Exchange transfusion with fresh heparinized blood is a safe procedure. Acta Pediar Scand 1985; 74: 360-5.
19. Dikshit SK, GeptaPK. Exchange transfusion in neonatal hyperbilirubinemia. Indian Pediatr 1989; 26: 1139-45.
20. Costarino AT, Ennever JF, Baumgart S, Spect WT, Paul M, Polin RA. Bilirubin photoisomerization in premature neonates under low and high dose phototherapy. Pediatrics 1985; 75: 519-22.

เปรียบเทียบประสิทธิภาพของการส่องไฟแบบสองด้านกับการส่องไฟแบบด้านเดียว

ประชา นันท์นฤมิต, พ.บ., ชลธิศ นาคา, พ.บ.**

ภาวะตัวเหลืองเป็นปัญหาที่พบบ่อยในทารกแรกเกิด จำเป็นต้องให้การวินิจฉัยโดยเร็วเพื่อป้องกันภาวะ bilirubin encephalopathy การส่องไฟเป็นวิธีที่ใช้แพร่หลายและมีประสิทธิภาพ ซึ่งประสิทธิภาพในการส่องไฟขึ้นกับแหล่งกำเนิดแสงที่ใช้ พลังงานแสงและพื้นที่ผิวสัมผัสกับแสง มีการศึกษาในต่างประเทศจำนวนมาก ใช้การส่องไฟโดยใช้ fiber-optic blanket ร่วมกับ convential phototherapy พบว่า สามารถลดระดับบิลิรูบินได้ดีโดยเฉพาะในทารกแรกเกิดก่อนกำหนด แต่ผลไม่ชัดเจนในทารกแรกเกิดครบกำหนด ในประเทศไทยมีการศึกษาค่อนข้างน้อย และ fiber-optic blanket หรือ bili-bed มีราคาแพง ผู้วิจัยจึงสนใจทำการศึกษาถึงประสิทธิภาพของการส่องไฟแบบสองด้านโดยใช้เครื่องมือที่ประดิษฐ์ขึ้นเอง

วัตถุประสงค์ : เพื่อศึกษาประสิทธิภาพและผลข้างเคียงการส่องไฟแบบสองด้านโดยใช้เครื่องมือที่ประดิษฐ์ขึ้นเอง เทียบกับการส่องไฟแบบด้านเดียวในทารกแรกเกิดครบกำหนด

วิธีการศึกษา : prospective randomized controlled trial ในกลุ่มทารกแรกเกิดครบกำหนดตัวเหลือง ที่หอผู้ป่วยทารกแรกเกิด โรงพยาบาลมหาราชนครราชสีมา ตั้งแต่เดือนกรกฎาคม 2543 ถึง เดือนเมษายน 2544

ผลที่ต้องการศึกษา : Primary outcome 1) อัตราการลดลงของระดับบิลิรูบินในแต่ละวัน 2) ระยะเวลาในการส่องไฟ 3) ผลข้างเคียงจากการส่องไฟ Secondary outcome อัตราการเปลี่ยนถ่ายเลือดหลังการส่องไฟในแต่ละวิธี

การวิเคราะห์ข้อมูล : Comparative analysis : Students' *t*-test

ผลการศึกษา : มีทารกแรกเกิดตัวเหลืองที่ทำการศึกษา 51 ราย โดย 24 รายส่องไฟแบบสองด้าน และ 27 รายส่องไฟแบบวิธีด้านเดียว ลักษณะของกลุ่มประชากรทั้งสองกลุ่มไม่ต่างกัน ยกเว้นกลุ่มที่ส่องไฟแบบสองด้านมีอายุที่เริ่มส่องไฟและระดับบิลิรูบินสูงกว่า ส่วนใหญ่ไม่พบสาเหตุของภาวะตัวเหลือง เมื่อเปรียบเทียบระหว่างกลุ่มที่ส่องไฟแบบสองด้านและด้านเดียวพบว่าอัตราการลดลงของระดับบิลิรูบินในวันแรกเป็น 0.22 $\pm$ 0.12 มก/ดล/ชม และ 0.14 $\pm$ 0.1 มก/ดล/ชม ตามลำดับ (p=0.02) อัตราการลดลงของระดับบิลิรูบินในวันที่สองเป็น 0.16 $\pm$ 0.11 มก/ดล/ชม และ 0.1 $\pm$ 0.05 มก/ดล/ชม ตามลำดับ (p=0.06) ระยะเวลาในการส่องไฟเป็น 34.9 $\pm$ 12.6 ชั่วโมง และ 43.7 $\pm$ 17.5 ชั่วโมง ตามลำดับ (p=0.039) ไม่พบว่ามีความแตกต่างของผลข้างเคียงในเรื่องไข้ อุจจาระ และน้ำหนักที่เปลี่ยนแปลงระหว่างสองกลุ่มและไม่พบว่ามีปัญหาจากการใช้เครื่องมือในระหว่างการศึกษา ไม่มีทารกแรกเกิดรายใดต้องทำการเปลี่ยนถ่ายเลือด

สรุปผลการศึกษา : การรักษาภาวะตัวเหลืองในทารกแรกเกิดครบกำหนด พบว่าการส่องไฟแบบสองด้านโดยใช้เครื่องมือที่ประดิษฐ์เองสามารถลดระดับบิลิรูบินดีกว่า ใช้ระยะเวลาในการส่องไฟน้อยกว่า และไม่พบว่ามีผลข้างเคียงเมื่อเทียบกับการส่องไฟแบบด้านเดียว

คำสำคัญ : การส่องไฟแบบสองด้าน, ภาวะตัวเหลืองในทารก

ประชา นันท์นฤมิต, ชลธิศ นาคา
จดหมายเหตุทางแพทย์ ฯ 2545; 85 (ฉบับพิเศษ 4): S1159-S1166

* ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400