How to Cite:
Dinatha, R. B., Utomo, M. T., & Setyoboedi, B. (2022). Intensive phototherapy as the initial management of severe hyperbilirubinemia in neonates: A literature review. *International Journal of Health Sciences*, *6*(S9), 2813–2831. https://doi.org/10.53730/ijhs.v6nS9.13083

Intensive phototherapy as the initial management of severe hyperbilirubinemia in neonates: A literature review

Rizaldo Bagoes Dinatha
Department of Child Health, Faculty of Medicine, Airlangga University,
Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Martono Tri Utomo
Department of Child Health, Faculty of Medicine, Airlangga University,
Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Corresponding author email: mrmartono73@gmail.com

Bagus Setyoboedi
Department of Child Health, Faculty of Medicine, Airlangga University,
Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

***Abstract*---**Hyperbilirubinemia is one of the most common clinical phenomena found in newborns, which is about 60% of term infants and 80% of preterm infants in the first week of life. Severe hyperbilirubinemia can cause encephalopathy and permanent neurodevelopmental damage with an incidence that varies between 4% - 60.3% and mortality rate of 13% to 56.8% worldwide. Phototherapy and exchange transfusion are therapeutic modalities for infants with severe hyperbilirubinemia. Intensive phototherapy has fewer side effects and can reduce the need for exchange transfusion. This treatment is rarely needed if intensive phototherapy is effective, current guidelines for the management of hyperbilirubinemia focus on the use of intensive phototherapy as initial treatment. This literature review aims to discuss intensive phototherapy as the initial management of severe hyperbilirubinemia in neonates.

***Keywords*---**Severe hyperbilirubinemia, intensive phototherapy, exchange transfusion, treatment, neonates.

Introduction

Hyperbilirubinemia is one of the most common clinical phenomena in newborns.[1] Approximately 60% of term infants and 80% of preterm infants suffer from

jaundice in the first week of life.[2] Severe hyperbilirubinemia can cause bilirubin encephalopathy and then kernicterus, which in turn will cause permanent neurodevelopmental damage.[3] In the United States, as many as 65% of newborns develop jaundice in the first week of life.[3] Several countries in Africa report that the incidence of severe hyperbilirubinemia varies from 17.7% to 60.3% with a mortality rate of 13% to 56.8%. In Asia, especially in developing countries, the incidence of severe hyperbilirubinemia is in the range of 4% to 46%.[4,5] Phototherapy is a safe and effective therapeutic modality for infants with severe hyperbilirubinemia, aiming to control serum bilirubin levels so that they do not reach values that can cause bilirubin encephalopathy and then kernicterus.[3] Phototherapy has fewer side effects and can reduce the need for exchange transfusion.[7] Exchange transfusion is a rapid method of reducing high serum bilirubin concentrations. This treatment is rarely needed if intensive phototherapy is effective, current guidelines for the management of hyperbilirubinemia focus on the use of intensive phototherapy as initial therapy.[8] This literature review aims to discuss intensive phototherapy as the initial management of severe hyperbilirubinemia in neonates.

Severe Hyperbilirubinemia in neonates

Hyperbilirubinemia is an increase in total bilirubin levels in the first week of birth, in adults it will appear when the serum bilirubin is >2 mg/dL (>17 mmol/L), whereas in neonates it is only seen when the serum bilirubin is >5 mg/dL (>86 mmol/L).[9] Formation of bilirubin that occurs in the reticuloendothelial system, then released into the circulation where it will bind to albumin. When red blood cells undergo hemolysis, hemoglobin is released. In the reticuloendothelial system, heme is converted by heme oxygenase to biliverdin and carbon monoxide. Furthermore, biliverdin is converted by biliverdin reductase into indirect bilirubin. Indirect bilirubin binds to albumin and is transported to the liver.[10]

Kernicterus is a state of bilirubin toxicity, which is a chronic and permanent neurological sequel. If the TSB (Total serum bilirubine) level is more than 25 mg/dL without signs of hemolysis, acute bilirubin toxicity should be considered.10 Acute bilirubin toxicity occurs in three phases during the first week after birth. The first phase occurs 1-2 days after birth which causes the baby to become lazy to drink, shrill cries, decreased consciousness, hypotony to seizures. The second phase occurs in the middle of the first week after birth and results in hypotonia of the extensor muscles, opisthotonos, retrocollis and fever. The third phase occurs after the first week of birth and causes hypotonia. If the bilirubin concentration is not lowered, BIND (Bilirubin-induced Neurological Dysfuntion) will occur. Neuronal damage usually occurs in the basal ganglia and brainstem nuclei, but damage can also occur in the hippocampus and cerebellum.[13]

Severe hyperbilirubinemia when the total serum bilirubin value is more than 25 to 30 mg/dL (428-513 mmol/L) is associated with an increased risk of BIND which occurs when bilirubin crosses the blood-brain barrier and binds to brain tissue.[5] Severe hyperbilirubinemia is associated with significant morbidity and mortality, this is due to accumulation of bilirubin in the basal ganglia and brain stem nuclei causing kernicterus.[5] Causes of severe hyperbilirubinemia are

categorized as hemolytic (blood group incompatibility, sepsis, G6PD deficiency) or non-hemolytic (breastfeeding jaundice, internal bleeding, gestational diabetes, pyloric stenosis, hypothyroidism and multiple mutations in liver enzymes).[12] Prematurity, jaundice within the first 24 hours of life, history of jaundice before hospital discharge, history of jaundice receiving phototherapy in siblings and race Asia is another predisposing factor for severe hyperbilirubinemia.[12]

Intensive phototeraphy in neonates

Phototherapy is a therapeutic modality using blue light which is used for the treatment of hyperbilirubinemia (unconjugated) or jaundice in newborns. The goal of phototherapy is to control serum bilirubin levels so that they do not reach values that can lead to bilirubin encephalopathy or kernicterus.[2] Phototherapy will convert the bilirubin present in the superficial capillaries and intestinal spaces into a water-soluble isomer that can be extracted without further metabolism by the liver. Maisels, a bilirubin researcher, states that phototherapy is a percutaneous drug.[15] Light penetration increases with increasing wavelength, so phototherapy rays with a maximum energy range of 460-490 nm (as in blue light) are most effective.[15]

Clinically significant phototherapy toxicity has rarely been reported.[3] In infants with cholestasis (direct hyperbilirubinemia), phototherapy can produce the baby bronze syndrome, in which the skin, serum and urine darken and have a grayish-brown color.[17] Purpuric and bullous eruptions have also rarely been reported in infants with jaundice due to severe cholestasis undergoing phototherapy.[18,19] An erythematous rash may appear in infants treated with tin-mesoporphyrin (an experimental drug used to prevent and treat hyperbilirubinemia) and subsequent exposure to sunlight and fluorescent light.[19,20,21] Blistering and agitation during phototherapy can be symptoms of a congenital porphyria.[22,23,24] The effect of phototherapy on oxidative stress and its effect on antioxidant/oxidant balance over a period of time after conventional, LED (Light emitting diode), and fiberoptic phototherapy have been investigated and shown that phototherapy is indicated to disrupt oxidant/antioxidant balance and induce oxidative stress.[25,26,28] Effect of phototherapy on oxidative stress and its effect on antioxidant/oxidant balance over a period of time after conventional, LED, and fiberoptic phototherapy have been investigated and shown that phototherapy is indicated to disrupt oxidant/antioxidant balance and induce oxidative stress.[25,26,28]

According to American Academy of Pediatric (AAP) guidelines, intensive phototherapy is defined as the use of phototherapy with blue light (with a wavelength of 430-490 nm) delivered at 30 W/cm2/nm or more on the body surface. The dual phototherapy model is also known as intensive phototherapy which is given to neonates who experience a very rapid increase in serum bilirubin.[29,30,31] Blue super LEDs that emit high intensity, generate heat and use lower energy and have a longer lifespan, so they are considered more efficient for intensive phototherapy.[32] Recently developed Bilisphere360 is a new neonatal phototherapy device designed to provide blue light exposure to the entire surface of the baby's skin. Bilisphere360 is called the most effective intensive neonatal phototherapy with high irradiance levels and coverage area with a horizontal cylindrical chamber containing 16 20W/52 fluorescent blue TL tubes.[33]

Intensive phototherapy in neonates with severe hyperbilirubinemia

In 2007 a phototherapy system was developed using an LED that emits high-intensity blue light with a maximum peak level of 450 nm to later become the forerunner to the formation of a nanotechnology called Blue Super LED.[32] Study by Sherbiny et al 2016 assessed and compared therapeutic efficacy and safety of Blue super LED with conventional intensive phototherapy in the management of severe hyperbilirubinemia in neonates. In this study it was found that phototherapy success rates were significantly higher in neonates in the hemolytic and non-hemolytic subgroups treated with Blue super LED phototherapy compared to those treated with conventional intensive phototherapy (87% vs 64%, P = 0.003.[32] Study by Azlin 2011 compared the decrease in bilirubin levels in single phototherapy with multiple phototherapy (intensive) with a total sample of 60 divided by 30 samples in each group (group I single phototherapy and group II dual phototherapy) diagnosed with hyperbilirubinemia according to the APP criteria. The results of the study it was found that intensive (double) phototherapy produced a larger beam and was more effective in reducing bilirubin levels in neonates with hyperbilirubinemia compared to single phototherapy. single phototherapy.[31]

Study by Osama El Feky et al 2016 assessed the effectiveness of intensive phototherapy in lowering bilirubin levels in neonates and reducing the need for exchange transfusion (ET) and duration of phototherapy over a 7 month period reported that of 200 neonates with hyperbilirubinemia based on APP criteria were divided into 2 groups showed a statistically significant difference in the decrease in bilirubin levels after assessment at 12-48 hours of phototherapy (decreased rate of 6.6mg / dl (21.3%) for the bilisphere group vs. 3.5 mg / dl (11.4%) for the control, p = 0.05).[43] The same study was previously conducted by Amira Abdel et al in 2014 with a sample size of which is more, namely 360 neonates in the observation period of 4 months, the result is that there is a statistically significant difference in p there was a decrease in bilirubin levels after assessment at 12-48 hours of phototherapy (rate of reduction 6.1mg/dl (21.4%) for the bilisphere group vs. 3.6mg/dL (11.4%) for the control, p=0.05) . In this study the Bilisphere group also showed a shorter duration of phototherapy than the control group (mean 2.7 ± 1.5 days versus mean 4.2 ± 1.4). Another result was that 19 neonates (10.4%) in the bilisphere group required ET vs. 130 neonates (73.4%) in the control group.[44] Another study by Nashwan et al 2013 compared the effectiveness of intensive phototherapy with conventional phototherapy with a total sample of 252 neonates with hyperbilirubinemia who were observed for 12 months. In group I 142 hyperbilirubinemic neonates were treated with conventional phototherapy (three EXZ quartz halogen lamps emiETing white light of wavelength 400-520 nanometers having an intensity of at least 10 w/cm2/nm placed at 43 cm from the neonate) and in group II 110 hyperbilirubinemic neonates. treated with intensive phototherapy (Bilisphere 360). From this study, it was found that the mean rate of decrease in the percentage of TSB per hour in the first 6 and 6-12 hours after phototherapy was significantly greater in group II compared to group I. The mean percentage of TSB decreased in the second 12 hours after phototherapy among neonates in the group. II was significantly higher and the value was twice that of group I (43.45 ± 14.83 vs 17.03 ± 14.22; p < 0.001), respectively.[45]

Study by Yasser Ahmed et al in 2018 aimed to evaluate the effectiveness of intensive phototherapy using Bilisphere360 in severely hyperbilirubinemic neonates with a sample of 100 neonates who were observed for 6 months divided into 2 groups (hemolytic and non-hemolytic). The results showed no significant change between hemolytic and nonhemolytic jaundice regarding the hourly decrease in total bilirubin and direct bilirubin after 8 hours. This is in line with Abd-Ellatif's 2012 study which stated that of the total 212 neonates with severe hyperbilirubinemia who received intensive phototherapy with Bilisphere360, only 13 required exchange transfusion. In contrast to another study by De Carvalho in 2011 quoted from the 2012 Abd-Ellatif study which reported that of the 116 total samples with severe hyperbilirubinemia who received intensive phototherapy, none of them underwent exchange transfusion, this difference was due to the long duration of intensive phototherapy 35.4 ± 19, 5 hours compared to the study above only 8 hours. Quoted from the 2012 Abd-Ellatif study, Al-Hafidh's 2013 study also reported no neonates with severe hyperbilirubinemia who underwent exchange transfusion after receiving intensive phototherapy, this difference was related to lower baseline TSB levels (18.85±4.57mg/dl). Study by Abdelazeem KS et al 2017 compared the effectiveness of intensive phototherapy with conventional phototherapy in reducing the need for ET and duration of phototherapy in the management of severe hyperbilirubinemia in neonates. In this study the subjects were divided into 2 groups, group I received intensive phototherapy, and group II received conventional phototherapy and was observed for 11 months. The results of the study showed that the decrease in mean TSB after 6 hours of phototherapy was significantly higher in the intensive phototherapy group (0.56 ± 0.12 mg/dl/hour) than the control group (0.17 ± 0.05 mg/dL/hour). In this study, it was also found that intensive phototherapy shortened the duration of hospitalization in hyperbilirubinemic patients, the average duration of phototherapy in group I was 2.5 ± 1.5 days compared to group II 4.0 ± 1.4 days. Other results also showed that the need for ET in group I was only 16 neonates (32%) compared to 31 neonates (62%) in group II.[47]

A study by Saboute et al 2017 assessed the effect of intensive phototherapy on reducing TSB levels to reduce patient morbidity, with a sample size of 40 per group divided into 4 groups divided based on the etiology of hyperbilirubinemia observed for 2 years (2014-2016). To determine the effect of intensive phototherapy on reducing TSB levels, subjects were divided into 2 groups of neonates with a bilirubin level of more than 14 mg/dl and less or equal to 14 mg/dl. Intensive phototherapy was administered according to AAP criteria, with measurement of TSB levels evaluated 6 and 24 hours after phototherapy was started. The results showed that the mean level of bilirubin reduction after 6 and 24 hours of intensive phototherapy was 4 and 6.2 mg/dl, respectively, TSB levels after 6 hours of intensive phototherapy decreased more significantly in neonates with TSB levels of more than 14 mg/dl than TSB levels. less than equal to 14 mg/dl.[48] A recent study by Guetta al 2019 which compared the rate of reduction in TSB levels in hyperbilirubinemic neonates receiving LED phototherapy with conventional phototherapy. The study was conducted for 2 years in a hospital in India with a total sample of 166 neonates divided into 2 equal groups (LED phototherapy group and conventional phototherapy group), neonates with need for ET, ventilator, <35 weeks, culture positive with clinical sepsis were excluded from the study. in this journal. The results showed that the mean reduction in

TSB was higher in the LED phototherapy group compared to the conventional phototherapy group. From the above study it was concluded that LED phototherapy has a faster rate of reduction in TSB compared to conventional phototherapy in neonatal hyperbilirubinemia.[49]

Conclusion

Hyperbilirubinemia is one of the most common clinical phenomena found in newborns. It is said to be severe hyperbilirubinemia if the total serum bilirubin level is more than 25 to 30 mg/dL and then it can develop to cause bilirubin encephalopathy then kernicterus and cause permanent neurodevelopmental damage. Phototherapy is a therapeutic modality used for neonates with hyperbilirubinemia that is safe and effective for controlling serum bilirubin levels. Intensive phototherapy is phototherapy with waves 430-490 nm delivered at 30 W/cm2/nm or more on the body surface. Various studies have shown that intensive phototherapy is very effective in reducing TSB compared to conventional phototherapy, intensive phototherapy can also significantly shorten the duration of hospital stay, and the need for ET in neonates with severe hyperbilirubinemia.

Conflict of Interest

The authors do not decleare any financial or personal links to other persons or organization that could adversely affect the content of this publication or claim rights thereto

Acknowledgements

We thank Martono Tri Utomo, MD, Ph.D (Universitas Airlangga, Dr Soetomo General Academic Hospital) and Bagus Setyoboedi, MD, Ph.D (Universitas Airlangga, Dr Soetomo General Academic Hospital) for providing guidance and insightful discussions in completing this paper

References

1. Stoll BJ & Kliegman RM. Jaundice and hyperbilirubinemia in the newborn. In: Behrman RE, Kliegman RM & Jenson HB, editors. *Nelson textbook of pediatrics*. 17th ed. Philadelphia: Saunders; 2006.
2. Harianto A, Etika R, Utomo MT, Angelika D, Handayani KD & Sampurna MTA. Hiperbilirubinemia pada neonatus. Surabaya: Dept/SMF Ilmu Kesehatan Anak FK Unair/RSU Dr. Soetomo; 2014.
3. Maisels MJ. Phototherapy--traditional and nontraditional. *J Perinatol.* 2001;211:93-7.
4. Hta I. Tata laksana ikterus neonatorum. Jakarta: Unit pengkajian teknologi kesehatan direktorat jenderal pelayanan medik departemen kesehatan RI; 2014.
5. Greco C, Arnold G, Nem-Yun-Boo, Iskander IF, Okolo AA, Rohsiswatmo R, Shapiro SM, Watchko J, Wennberg RP, Tribelli C, ZabeETa CD. Neonatal jaundice in low and middle income countries: lessons and future directions from the 2015 don ostrow trieste yellow retreat. *Neonatology*. 2016;110:172-80.

6. Sampurna TAM, Ratnasari KA, Saharso D, Bos AF, Sauer PJJ, Dijk PH, Hulzebos CV. Current phototherapy pratice on java, indonesia. *BMC Pediatrics*. 2019;19:188-94.
7. Steiner LA, Bizzarro MJ, Ehrenkranz RA & Gallagher. P. G. A decline in the frequency of neonatal exchange transfusions and its effect on exchange-related morbidity and mortality. *Pediatrics*. 2007;120:27-32.
8. Bergman DA, Cooley JR, Coombs JB, Goldberg MJ, Homer CJ, Nazarian LF & Riemenschneider TA. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. American Academy of Pediatrics. Provisional CommiETee for Quality Improvement and SubcommiETee on Hyperbilirubinemia. *Pediatrics.* 1994;94:558-65.
9. Ramasethu J. Neonatal hyperbilirubinemia. Neonatal Intensive Care. Jakarta: RSAB Harapan Kita; 2002.
10. Watchko JF & Maisels MJ. Jaundice in low birthweight infants: pathobiology and outcome. *Arch Dis Child Fetal Neonatal Ed.* 2003;88: 455-8.
11. Ambalavanan N & Carlo WA. Jaundice and hyperbilirubinemia in the newborn. In: Behrman RE, Kliegman RM & Jenson HB, editors. *Nelson Textbook of pediatrics*. 20th ed. Philadelphia: Saunders; 2015.
12. Porter ML & Dennis BL. Hyperbilirubinemia in the term newborn. *Am Fam Physician.* 2002;65:599-606.
13. Smitherman H, Stark AR & Bhutani VK. Early recognition of neonatal hyperbilirubinemia and its emergent management. *Semin Fetal Neonatal Med. 2006;*11:214-24.
14. Bhutani VK & Wong RJ. Bilirubin neurotoxicity in preterm infants: risk and prevention. *Journal of Clinical Neonatology. 2013;*2:61-69.
15. Maisels MJ & Mcdonagh AF. Phototherapy for neonatal jaundice. *N Engl J Med.* 2008;358:920-8.
16. Vreman HJ, Wong RJ & Stevenson DK. Phototherapy: current methods and future directions. *Semin Perinatol.* 2004;28:326-33.
17. Rubaltelli FF, Jori G & Reddi E. Bronze baby syndrome: a new porphyrin-related disorder. *Pediatr Res.* 1983*;*17:327-30.
18. Paller AS, Eramo LR, Farrell EE, Millard DD, Honig PJ & Cunningham BB. Purpuric phototherapy-induced eruption in transfused neonates: relation to transient porphyrinemia. *Pediatrics.* 1997*;*100:360-4.
19. Valaes T, Petmezaki S, Henschke C, Drummond GS & Kappas A. Control of jaundice in preterm newborns by an inhibitor of bilirubin production: studies with tin-mesoporphyrin. *Pediatrics.* 1994;93:1-11.
20. Tonz O, Vogt J, Filippini L, Simmler F, Wachsmuth ED & Winterhalter KH. Severe light dermatosis following photo therapy in a newborn infant with congenital erythropoietic urophyria. *Helv Paediatr Acta.* 1975;30:47-56.
21. Yahia S, Shabaan AE, Gouida M. Influence of hyperbilirubinemia and phototherapy on markers of genotoxicity and apoptosis in full-term infants. *Eur J Pediatr.* 2015;174:459-464.
22. Procianoy RS, Silveira RC, Fonseca LT, Heidemann LA, Neto EC. The influence of phototherapy on serum cytokine concentrations in newborn infants. *Am J Perinatol.* 2010;2:375-379.
23. Zarkesh M, Dalili S, Fallah MJ, Heidarzadeh A, Rad AH. The effect of neonatal phototherapy on serum, level of interleukin-6 and white blood cell's count. *J Clin Neonatol.* 2016;5:189-192.

24. Rashedy FH, El-Hawy MA, Helwa MA, El-Shahat MI. Effect of phototherapy on CD4, CD8 and natural killer cells of full term neonates with indirect hyperbilirubinemia. *Egypt J Immunol*. 2015;22:23-29.
25. Elfeky RAA, FaETah MAA, Gaafar DM, Afifi HA. The effect of phototherapy on lymphocyte subsets in newborn infants. *J Allergy Clin Immunol*. 2012;129:12-16.
26. Demirel G, Uras N, Celik IH. Comparison of total oxidant/antioxidant status in unconjugated hyperbilirubinemia of newborn before and after conventional and LED phototherapy: a prospective randomized controlled trial. *Clin Invest Med*. 2010;33:335-41.
27. Sedlak TW & Snyder SH. Bilirubin benefits: cellular protection by a biliverdin reductase antioxidant cycle. *Pediatric*. 2004;113:1776-82.
28. Kale Y, Aydemir O, Celik U. Effects of phototherapy using diferent light sources on oxidant and oxidant status of neonates with jaundice. *Early Hum Dev*. 2013;89:957-60.
29. Dahlquist G & Kallen B. Indications that phototherapy is a risk factor for insulin-dependent diabetes. *Diabetes Care. 2*003;26:247-8.
30. Aspberg S, Dahlquist G, Kahan T & Kallen B. Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? *Pediatr Allergy Immunol.* 2007;18:313-9.
31. Azlin E. Efektifitas fototerapi ganda dan fototerapi tunggal dengan tirai pemantul sinar pada neonatus yang mengalami Jaundice. *Sari Pediatri*. 2011;13:111-6.
32. Sherbiny HS, Youssef DM, Sherbini AS, El-Behedy R, Sherief LM. High-intensity light-emeETing diode vs flourescent tubes for intensive phototherapy in neonates. *Paediatrics and International Child Health*. 2016;36:127-3.
33. Bandyopadhyay A, Maiti R. Acute management extreme neonatal jaundice the potential benefits of intensified phototherapy and interruption of enterohepatic bilirubin circulation. *Int Journal of Pediatric*. 2017;4:853-57.
34. Ebbesen F, Agati G & Pratesi R. Phototherapy with turquoise versus blue light. *Arch Dis Child Fetal Neonatal Ed.* 2003;88:430-5.
35. Cremer RJ, Perryman PW & Richards DH. Influence of light on the hyperbilirubinaemia of infants. *Lancet*. 1958;1:1094-97.
36. Ennever JF, Mcdonagh AF & Speck WT. Phototherapy for neonatal jaundice: optimal wavelengths of light. *J Pediatr.* 1983;103:295-9.
37. Jansen PL. Diagnosis and management of crigler-najjar syndrome. *Eur J Pediatr.* 1999;158:89-4.
38. Kosim MS, Soetandio R, Sakundarno M. Dampak lama fototerapi terhadap penurunan kadar bilirubin total pada Hiperbilirubinemia Neonatal. *Sari Pediatri*. 2008;10:201-6.
39. Bansal A, Jain S, Parmar VR, Chawla D. Bilirubin rebound after intensive phototherapy for neonatal jaundice. *Indian Pediatri*. 2009;47:607-9.
40. Sanpavat S. Exchage transfusion and it's morbidity in ten year period at king khulalongkom hospital, *J Med Assoc Thai.* 2005;88:588-92.
41. Slusher T, Wong RJ, Vreman HJ & Stevenson D. Selectively filtered sunlight phototherapy is safe and efficacious for treatment of neonatal jaundice in nigeria. *American Academy of Pediatrics National Conference and Exhibition.* 2012;87:281-6.

42. American Academy of Pediatrics SubcommiETee on H. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297–316.
43. Osama A, Amir M, Ahmad A, Mohammed G. The role of intensive phototherapy device in treatment of neonatal jaundice. *Med J Cairo Univ*. 2016;84:271-5.
44. Amira Abdel FE, Eman Abdel G, Abdel Rahman AR, Amary MZ. The role of intensive phototherapy device in decreasing the need for exchage transfusion in neonatal jaundice. *Med J Cairo Univ*. 2014;64:64-5.
45. Nashwan MA, Ziad KA, Ruthwan SS. Double-surface intensive phototherapy vs single-surface conventional phototherapy in treatment of neonatal hyperbilirubinemia. *Ann Coll Med Mosul*. 2013;39:25-31.
46. Yasser AA, Yaser TK, Samar ANI. Effect of intensive phototherapy on bilirubin induced neurological defect (BIND) score in neonates with severe hyperbilirubinemia.*The egyptian journal of hospital medicine*. 2019;74:1643-48.
47. Abdelazeem KS, Soliman AA, Askar EAA. Efficacy of intensive phototherapy in management of neonatal hyperbilirubinemia in neonatal unit of assiut university children hospital. *J Neonatal Biol*. 2017;6:266-9.
48. Saboute M, Mazouri A, Khalesi N, Nejad NH, Razaghian A. The effect of intensive phototherapy on management of hyperbilirubinemia in neonates with the gestational age of 34 weeks and more. *Iranian Journal of Neonatology*. 2017;8:1:83-8
49. Guetta S, Shenoy J, Kamath SP, Mithra P, Baliga BS, Sarcangala M, Srinivasan M. Light emitting diode (LED) phototherapy vs conventional phototherapy in neonatal hyperbilirubinemia: a single blinded randomized control trial from coastal india. *BioMed Research International*. 2019;62:1-6.