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Review Article

Side Effects of Phototherapy in Neonatal Hyperbilirubinemia

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Abstract

Phototherapy is a simple treatment for neonatal hyperbilirubinemia, it is well documented, and leads to greatly reduced exchange transfusion rates. The effectiveness of phototherapy is dependent upon: Color of the light, intensity of the light, exposed body surface area, and duration of exposure. It is a safe and easily available treatment worldwide and the side effects are not serious. The short-term side effects of phototherapy include interference with maternal-infant interaction, imbalance of thermal environment and water loss, electrolyte disturbance, bronze baby syndrome and circadian rhythm disorder. In addition, it may be associated with long-term side effects such as melanocytic nevi, allergic diseases, and retinal damage. This review article is particularly focused on the early and late side effects after phototherapy in neonatal hyperbilirubinemia.

Keywords: Neonate; Phototherapy; Hyperbilirubinemia; Side Effect

Introduction

Phototherapy is the use of visible light for treatment of hyperbilirubinemia in neonates. It is a non-invasive, safe and effective alternate to exchange transfusion. Hence, it has become the initial choice of treatment for hyperbilirubinemia in neonates [1]. The conjugated bilirubin is converted by structural photoisomerization and photo oxidation into water soluble products that can be excreted without conjugation by the liver [1,2]. This conversion not only occurs in the skin but also in the capillaries of the subcutaneous tissue. Approximately 60% of term babies and 85% preterm babies will develop clinically apparent jaundice, which classically becomes visibly apparent on day 3, peaks between days 5-7, and resolves by 14 days of age. Phototherapy treatment is indicated to prevent the neurotoxic effects of high serum unconjugated bilirubin. The American Academy of Paediatrics [AAP] has established guidelines for initiating phototherapy, based on age of newborn, serum total bilirubin levels, gestational age, and individual risk factors [3]. A commonly used rule of thumb for initiating phototherapy is to start phototherapy when the total serum bilirubin in five times the weight. For example, a 3kg baby when bilirubin levels are 15 mg/dl and in 4 kg neonate when levels are 20mg/dl [2]. Phototherapy is continued until serum bilirubin values fall within normal of the jaundice graph. Phototherapy is contraindicated in direct hyperbilirubinemia, porphyrias, and neonates with a history of photosensitive drug history. The dose of phototherapy determines how effectively it works, and is determined by the wavelength of the light, the intensity of the light [irradiance], the distance between the light and the infant, and the body surface area exposed to the light [1].

Light from visible spectrum is used for phototherapy. This light is usually filtered from harmful UV rays before exposing the baby to it. Sunlight, though effective, is not filtered and may be harmful for babies. White light and blue-green spectrum is commonly employed. Blue light has better penetrance, antibacterial activity, and is also well absorbed by bilirubin for photoisomerization. The AAP recommends light with wavelength 460-490 nm [3]. The intensity of light [irradiance] is the number of photons delivered per centimetre squared of body surface area and is measured by spectral radiometry. Irradiance is ideally measured at several sites under

the area illuminated due to spatial variations in intensity and measurements should be averaged. The AAP recommends that the irradiance be checked at least under the centre of light source. The effectiveness of phototherapy can be determined by the spectral power of phototherapy, which in turn depends on the irradiance and the body surface area; [ie] the larger the body surface area and the stronger the light, means higher spectral power in phototherapy [3-5].

Types of phototherapy and lights used in phototherapy

There are currently 2 types of phototherapy devices available: conventional phototherapy and fiberoptic devices.

Conventional phototherapy uses different bulbs such as halogen bulb, metal halide gas discharge tubes, fluorescent bulbs, and LEDs. The light source is usually placed above or below the baby and the distance between the baby and the light source determines the irradiance. This distance varies between different machines. Fiberoptic phototherapy usually uses the quartz halogen bulb. The light from the bulb is passed through a filter before being transmitted to fiberoptic cables weaved through blankets. These blankets are kept in contact with the neonate's skin. Light sources used in phototherapy are Quartz halogen bulb, metal halide gas discharge tubes, fluorescent bulbs (long, compact or folded), and LEDs. Fluorescent light bulbs are the most common type of light bulb used. They can be long bulbs or compact or folded bulbs. White and blue fluorescent bulbs are used. They are relatively inexpensive, but the irradiance decreases with time.

Quartz halogen bulbs appear white and have a broad output range with yellow and red components. They tend to heat quickly, and filtration may be required before phototherapy. The intensity does not decrease but they are fragile when hot and must be handled carefully. Gas discharge tubes are now obsolete. They produce a broad spectrum which appears blue- white.

LED lights should not decrease in intensity with age and are not fragile. They should produce less heat as their spectrum fall in the blue region of the light spectrum [5]. Phototherapy may be continuous or intermittent [phototherapy for an hour and off for an hour or on for 6 hours and off for 6 hours]. Single phototherapy uses only one phototherapy unit, double phototherapy uses two phototherapy units and triple phototherapy uses three phototherapy units. So triple phototherapy is expected to be more effective than double or single. Intensive phototherapy is delivering light with a spectral radiance of 30 microW/cm^2/nm or higher over as much body surface area as possible. The intensity of light delivered can be increased with use of reflective surfaces, aluminium foil and white cloth placed on the sides of the neonate. It is used to rapidly reduce bilirubin levels, proving useful in neonates with bilirubin levels high enough to produce neurological deficits [1].

Side effects of phototherapy

Side effects of phototherapy may be divided into short terms effects and long term effects.

Short term effects [5-7]

Interferes with maternal-neonate interaction

Phototherapy separates the child from the mother and interferes with maternal - child bonding. It can alter the neonate's auditory and visual alertness and make the parents anxious. Abrol P., *et al.* [8] reported that neonates who received phototherapy were significantly poorer in orientation response to visual inanimate, visual animate, and visual and auditory animates in cluster interactive processes. Olusanya BO., *et al*. [9] found that 36 % of mothers appreciated the use of filtered sunlight phototherapy as they get an opportunity to feed and bond with the child while receiving treatment was unlike when they have to be separated under conventional phototherapy. Interrupted phototherapy may have a significant role in increasing the maternal-neonatal interaction during phototherapy management and permit skin to skin contact and breastfeeding

Imbalance of thermal environment and hydration

The newborn is placed in diaper for maximum exposure and may develop hypothermia, if room temperature is not maintained, as phototherapy units are not designed to provide a comfortable thermal environment for the baby. High irradiance phototherapy can cause hyperthermia. It increases the blood flow in capillaries of the skin and muscles and can lead to overheating if the neonate is placed in a warmer or incubator during phototherapy. Brandão DC., *et al.* [10] mentioned that incidence of hypothermia was more in LED group than in the fluorescent group (23% versus 9%, $p = 0.02$). Another study conducted by Aydemir O., *et al.* [11] on body temperature changes of newborn under fluorescent versus LED phototherapy, in which the mean body temperature of newborn receiving LED phototherapy of 60-120 micro w/cm(2)/nm was higher ($p < 0.001$) from the other groups who received Fluorecent lamps (10-15 micro w/cm(2)/nm irradiance) and LED phototherapy of 26-60 micro w/cm(2)/nm irradiance. Conventional phototherapy changes the thermal environment of the neonate and may lead to

insensible water loss and dehydration with hyperthermia or hypothermia.

Loose motions

Some neonates may also have loose stools while on phototherapy, due to the irritation of the bowel by bilirubin, adding to water loss. Breast feeding should be continued when possible and fluid resuscitation should be started if required. A study on insensible water loss from skin during phototherapy in term and preterm neonates by S Kjartansson., *et al.* [12], measured the rate of evaporation of water from the skin. The water vapour gradient close to the surface of the skin was used to determine the water loss. It was found to be the same before and after 30 minutes of phototherapy in a term neonate, whereas in preterm, the value was 9.8g/m^2, 2 hours before phototherapy and 9.7g/m^2 2 hours after phototherapy. Another study conducted by Maayan-Metzger A., *et al*. [13] on transperineally water loss and skin hydration in preterm infants during phototherapy, the mean increase in trans epidermal water loss was 26.4% during phototherapy, most prominent increases were recorded from cubital fossa then groin and then back.

Electrolyte disturbances

De Curtis M., *et al.* [14] studied that clear inhibition of absorption of water and electrolytes was seen in jaundiced infants receiving phototherapy because of intestinal secretion.

Hypocalcemia

Phototherapy changes the secretion cycle of melatonin from the pineal gland, by altering the circadian rhythm. Melatonin is called the hormone of darkness and peak release occurs at night. Brain illumination in phototherapy reduces the melatonin levels. The decreased levels of melatonin in the blood can cause hypocalcemia. Melatonin has been found to promote bone formation and decrease bone resorption, increase the activity and differentiation of osteoblastic cells, and decrease osteoclastic activity and differentiation. Increased urinary excretion of calcium during phototherapy may also attribute to hypocalcemia. Khan M., *et al.* [15] in their study they noted 22.76% (28/123) of term neonates exhibited phototherapy induced hypocalcemia. Another study by Bahbah., *et al.* [16] done in 2014 in Egypt reported that 26% term neonates who received phototherapy for jaundice developed hypocalcemia after 48 hours of phototherapy. Gheshmi AN., *et al*. [17] reported a decrease in the serum calcium concentration in 54% of full-term neonates after phototherapy.

Changes in circadian rhythm

The changes in circadian rhythm due to phototherapy may cause jitteriness, altered heart rate, and increased crying among neonates. Phototherapy should be given in parallel to circadian cycle if possible. In a study conducted by Chen A., *et al*. [18] on effect of blue light exposure on expression of circadian genes, the result showed that the expression of Bmal1 gene was decreased and Cry1 gene increased significantly after phototherapy, but there was no statistical difference from the control group. Another study conducted by Martin Cremer., *et al*. [19] on immediate effects of phototherapy on sleep in very preterm neonates found no differences in sleep cycle duration during phototherapy ($p = 0.405$).

Bronze baby syndrome (BBS)

This condition is found in neonates with biliary cholestasis undergoing phototherapy, where the skin, urine and serum develop a dark greyish-brown discolouration. The pathogenesis of the condition is not known but the discolouration resolves few days after stopping phototherapy [5,6]. All babies who develop this coloration should be evaluated for liver pathology. Shiva Prasad G., *et al*. [20] reported a case of bronze baby syndrome, who had a greyish brown discoloration of the entire body, which developed after starting phototherapy, and disappeared 3 weeks after discontinuation of phototherapy. A study conducted by Clark CF., *et al.* [21] on the postmortem data in a BBS cases suggest that the photo decomposed pigmented products of bilirubin are unable to pass the blood brain barrier, so the need for establishing the cause of jaundice prior to initiation of phototherapy should be evaluated.

Bullous and purpuric eruptions

Neonates with cholestasis undergoing phototherapy may develop bullous rash due to circulating levels of porphyrins. Purpuric lesions may develop in exposure areas within 24 hours after initiation of treatment. These usually resolve one week after discontinuation of phototherapy. Paller AS., *et al.* [22] studied the clinical and histological characteristics of the eruption, as well as the porphyrin levels in affected neonates. They concluded that the distribution of eruption in areas exposed to light and presence of circulating porphyrins suggest that porphyrinemia may underlie the light induce purpuric eruption. LaRusso J., *et al.* [23] reported a neonate who also had hemolytic disease of newborn, received intravenous immunoglobulin, and subsequently developed a purpuric eruption after visible light therapy.

Riboflavin deficiency

Riboflavin is found in all cells of the body and is degraded by phototherapy. This may result in the deficiency of glutathione reductase in the erythrocytes and which in turn can cause red cell hemolysis. Term neonates rarely require supplementation with riboflavin during phototherapy. Gromisch DS., *et al.* [24] reported that 16 out of 21 neonate who were exposed to phototherapy developed riboflavin deficiency. Another study conducted by Amin HJ., *et al*. [25] assessed the riboflavin status by measuring flavin adenine dinucleotide saturation of erythrocyte glutathione reductase. They noted all the eight neonates exposed to phototherapy developed riboflavin deficiency.

DNA damage

Phototherapy can cause transient damage to DNA, through oxidative injury to the cell membrane, increasing lipid peroxidase products. This increases the free radicals which cause damage to DNA strands and may result in mutations over a course of time. El-Abdin MY., *et al.* [26] noted a significant increase in DNA fragmentation in circulating lymphocytes among cases compared to controls. After phototherapy it showed more statistically significant increase in DNA fragmentation compared to its level before phototherapy among cases. Tatli MM., *et al.* [27] determined DNA damage in lymphocytes by use of alkaline comet assay and reported that the DNA damage increased significantly with the duration of phototherapy ($p < 0.001$). Another study conducted by Aycicek A., *et al.* [28] reported that mean value of DNA damage scores in both the intensive and conventional phototherapy groups were significantly higher than those in control group ($p < 0.001$).

Haematological effects

Oxidative injury to RBC membrane may increase the fragility of the cells and can be a precipitating event for hemolysis in patients with hereditary spherocytosis. Mild to moderate asymptomatic thrombocytopenia may be seen in term neonates after 48 hours after initiating phototherapy. If bone marrow compensation of platelets is adequate, then no change is noted in the platelet count before and after phototherapy. Khera S., *et al*. [29] mentioned thatthe incidence of thrombocytopenia was seen in 35 (35%) neonates undergoing phototherapy. The majority of neonates had mild thrombocytopenia (74%). Moderate and severe thrombocytopenia was seen in 23% and 3% cases, respectively. Although the platelet counts decreased in the initial 48-72 hours after receiving phototherapy, in most of the cases, the platelet counts gradually increased after phototherapy was stopped. A study conducted by Aouthmany MM [30] measured the $ETCO_2$, which reflects hemoglobin degradation, the ETCO2 was significantly higher after 13.7+/-7.9 hours after starting phototherapy ($p < 0.05$).

Retinal damage

Phototherapy can cause photochemical lesions on the retina, as rhodopsin absorbs the light and triggers lipid peroxidation, and apoptosis of cells. The retina has greater susceptibility to blue light than to green light. Kernt M., *et al.* [31] reported that light exposure induced structural damage, decreased retinal pigment epithelium cell viability and increased reactive oxygen species. Thomas RC Sisson., *et al*. [32] assessed the effect of blue fluorescent light on retinas of a pigmented piglet and found that the high intensity blue fluorescent light was shown to damage the retinas of newborn piglets.

Long term side effects [5,7]

Increased incidence of allergic diseases

Increased incidence of allergic diseases is attributed to the fact that phototherapy may interfere with the switch from th2 to th1 response of immune system by increasing the levels of circulating inflammatory cytokines and because of damage to DNA of lymphocytes caused by phototherapy. UV radiation found in small amounts in the phototherapy reduce the circulating levels of CD4 lymphocytes, interferes with the activity of CD8 cells and natural killer cells, and may result in autoimmune diseases. Increasing unconjugated levels of bilirubin inhibit the complement cascade, prevent leukocyte migration and protects against oxidative stress. Inhibition of this function by phototherapy decreases the physiological effects of bilirubin, over th2 to th1 switching and may cause immune system dysfunctions, asthma, rhinitis and conjunctivitis, in later periods. Das RR., *et al.* [33] noted a significant increase in odds of asthma and allergic rhinitis after neonatal hyperbilirubinemia 4.26 (95% CI 4.04-4.5); 5.37(95% CI 4.16-6.92) respectively. Another study by F. Gloria-Bottini., *et al.* [34] concluded the positive relationship between phototherapy and allergy observed in the subjects studied at birth and after 30 years. The decrease of bilirubin level induced by phototherapy favours the oxidative stress resulting in an increased susceptibility to allergy.

Melanocytic nevi, melanoma and skin cancer

It has been postulated that the exposure of neonates to phototherapy may cause damage to mitochondrial and nuclear DNA and free radical production which may lead to future development of skin cancer. This is in part due to the small amount of UV radia-

tion found in blue spectrum of light. Further studies are required to firmly establish the correlation between phototherapy and skin cancer. Matichard E, *et al*. [35] noted that the number of nevi larger than 2 mm was significantly higher in cases exposed to phototherapy. The mean nevus count was 3.5 in exposed group and 1.45 in non-exposed group. Berg P., *et al*. [36] found none of the patients with childhood malignant melanoma had received phototherapy, in comparison with 11 of the controls. The difference was not significant (P = 0.08).

Ocular manifestations

Bilirubin plays a role as an anti-oxidant, hence decreasing resistance against oxidation and produces increased free radicals in both the retina and serum. This decreased oxidation resistance facilitates the development of Retinopathy of Prematurity [ROP]. It is therefore important to cover the eyes of the neonate during phototherapy. Uveal melanoma may also manifest in third and fourth decade. It has been postulated that blue light has increased penetrance as compared to UV light and can cause damage to the uveal tract during phototherapy or cell dysfunction and death. This can result in age related macular degeneration and contribute to tumor genesis, like uveal melanoma. Heyman., *et al*. [37] found that in neonates with ROP [stages 2, 3, or 4] bilirubin levels from day 4 were considerably lower than those in neonates with stage 1 ROP or no ROP and suggested that bilirubin may have a protective effect in the prevention of ROP. In another study conducted by Dan D Gaton., *et al*. [38] the mean bilirubin level of the first 14 days was 5.95 mg/dl in babies with ROP as compared with 6.05 mg/dl in neonates without retinopathy; the difference had no statistical significance (p > 005).

Patent ductus arteriosus (PDA)

Photon absorption by the cells of the heart cause relaxation of the aortic smooth muscle through the nitric oxide system. Phototherapy also changes the hemodynamics of the heart, by increasing heart rate and decreasing the variability of heart rate and cardiac output. Phototherapy also reduces the mean arterial pressure and results in increased peripheral blood flow. All these factors together cause the ductus arteriosus to relax and remain open [5]. Benders MJ., *et al*. [39] noted that all infants had a closed ductus arteriosus at the time of enrolment into the study. In > 50% (14 out of 27) of the infants, the ductus arteriosus reopened during phototherapy. The study conducted by Guo-Sheng Liu., *et al.* [40] showed that the blood endothelin levels measured after 24 hours of phototherapy were higher than the pretreatment values, as were blood NO levels measured after 12 hours and 24 hours of phototherapy. Both increases were statistically significant ($P < 0.05$) in the GA ≤ 32 weeks group. In the GA > 32 weeks group, blood NO levels measured after 24 hours of phototherapy were higher than the pretreatment values; these changes were also statistically significant ($P < 0.05$).

Conclusion

Although phototherapy is the most common and widely accepted and an effective treatment method for hyperbilirubinemia, it is also associated with side effects, both short term and long-term effects. As the use of phototherapy to treat hyperbilirubinemia has increased in the recent years, all the long-term effects of phototherapy are not yet fully evaluated and require further studies. It is therefore prudent, to use photo therapy only when indicated with careful monitoring for any complications.

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