PHOTOTHERAPY AND ITS EFFECT ON SOME PHYSIOLOGICAL FUNCTIONS IN NEWBORNS

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Abstract

Phototherapy represents the most common therapeutic intervention at neonatology departments in the first days of life. The beneficial effects of light on the decrease of the serum bilirubin level were first described by Cremer et al. in 1950's (1). Since then phototherapy has been successfully used to treat severe hyperbilirubinaemia and has almost completely replaced exchange transfusion. Phototherapy is a relatively non-invasive method. However, along with decreasing bilirubin level, it can also influence some other functions: perfusion of organs, predominantly skin; peripheral vascular resistance; distribution of blood flow; heart activity and, thus, also systemic blood pressure along with breathing. A side component of applied light is a certain amount of heat which warms the body surface up and, therefore, the risk of exogenous overheating and increased water loss through the skin arise. Maternal-infant separation, modification of calcium homeostasis, disturbed circadian rhythm, or changes of the hemodynamics of various organ systems are only a few of the undesired effects which prove phototherapy not to be a treatment without any side effects. Careful indication of phototherapy is essential, particularly in premature infants.

Key words: neonate, hyperbilirubinaemia, phototherapy, phototherapy devices, side effects

INTRODUCTION

Approximately 1 out of 2 full term infants and 8 out of 10 premature infants develop icterus. Generally, it occurs between the second and fourth day of life and retreats spontaneously after 7–14 days. For the vast majority of newborns the serum concentration of bilirubin does not reach a level which would require treatment. Despite this fact bilirubin in the blood in some infants can reach a level which exposes them to an increased risk of acute and chronic encephalopathy (kernicterus). In such cases the decrease of serum bilirubin is inevitable for prevention of the development of undesired consequences of hyperbilirubinaemia. Phototherapy and exchange transfusion represent effective types of treatment (2).

Phototherapy, although relatively non-invasive, impacts the ordinary regime of newborns. A side component of the applied light is a certain amount of heat which warms the body surface up. Therefore, the risk of exogenous overheating of organism arises together with corresponding modifications of physiological functions. Loss of water through the skin increases, cardiac output decreases, and blood flow is redistributed (3).

MECHANISM OF PHOTOTHERAPY, INDICATIONS, CONTRAINDICATIONS

The positive effects of light on the decrease of serum bilirubin level of icteric newborns were first described by Cremer et al. in 1958 (1). Since then phototherapy has been used very effectively as a relatively financially undemanding and non-invasive treatment of neonatal hyperbilirubinaemia. Owing to the routine use of phototherapy in clinical practice the number of exchange transfusions has been decreased to minimum and exchange transfu-

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sion is used only as a prevention of the development of kernicterus in infants with serious hyperbilirubinaemia after phototherapy failure.

Bilirubin toxicity is usually seen in case of significant neonatal hyperbilirubinaemia and in patients with Crigler-Najjar syndrome. In newborns unconjugated bilirubin concentrations above 340 $\mu\text{mol/l}$ are considered dangerous. Kernicterus can also occur at lower levels, for instance in the presence of sulphonamides medication, radiographic contrast media, or antiinflammatory drugs that displace bilirubin from the albumin binding sites. Bilirubin is also an antioxidant so moderate hyperbilirubinaemia may have a prophylactic effect against some cardiovascular diseases (4).

The clinical manifestation of bilirubin toxicity is the development of acute bilirubin encephalopathy (ABE). In the early phase of ABE seriously jaundiced neonate become lethargic and hypotonic and suck poorly. The intermediate phase is typically accompanied by stupor, irritability, and hypertonia. The newborn baby may develop a fever with high-pitched cry, which can alternate with somnolency and hypotonia. The hypertonia is manifested by retrocollis and opisthotonus. Some authors think that an emergent exchange transfusion in some cases might reverse the central nervous system damage. The advanced phase when the central nervous system is irreversibly damaged is characterized by noticeable retrocollis, opisthotonus, harsh cry, poor feeding, apnea, fever, stupor to coma, seizures, and death (5).

The chronic form of bilirubin encephalopathy is kernicterus. Surviving children may develop a severe form of athetoid cerebral palsy, auditory disorders, enamel dysplasia, paralysis, intellectual and other handicaps (5).

The aim of neonatal healthcare during the first days of life is a thorough screening of neonatal icterus, identification of risk group of infants, especially those with haemolytic diseases with proven ABO or Rh incompatibility, and adequate treatment in indicated cases.

During the exposure of skin to light a photochemical conversion of native bilirubin occurs. The outcome of the conversion is the formation of several different products (6). Configurational isomerization takes place reversibly and considerably faster than structural isomerization which is irreversible and leads to the formation of lumirubin (Z-lumirubin, E-lumirubin). Lumirubin can be rapidly eliminated in liver and, therefore, transformation to lumirubin is considered to be the primary reason of the phototherapeutical effect. Photooxidation occurs too but considerably more slowly and is, thus, considered less significant (7). In newborns the formation of photoisomers commences practically immediately after turning the light on and a long time before significant changes in total serum bilirubin (TSB) can be proven in blood. Details of the metabolism of photoisomers are unknown. However, these products are more water-soluble and can be excreted by bile and urine and concurrently avoid conjugation in the liver (8).

A strong relationship occurs between the dose of phototherapy and the rate of decreasing in serum bilirubin level. Dose of phototherapy is determined by these factors:

1. *Spectral qualities of the light source*: the most effective wavelength range with the peak of 460 ± 10 nm; blue, green, and turquoise light are considered the most effective.

2. *Intensity of the light (irradiance)*: the number of photons delivered per square centimetre of exposed body surface; the higher the irradiance the faster the decline in serum bilirubin level; spectral irradiance could be measured with a spectral radiometer; intensive phototherapy requires a spectral irradiance of $30 \mu\text{W}/\text{cm}^2/\text{nm}$.

3. *Distance between the light and the infant's skin*: halogen lamps cannot be positioned closer to the infant than recommended without incurring the risk for a burn.

4. *Exposed body surface*: the greater the body surface area exposed to light the faster the decline in serum bilirubin (9).

The indications for initiation of phototherapy are guided by recommendation of American Paediatric Academy for management of hyperbilirubinaemia in the newborn infants 35 or more weeks of gestation (10). Bhutani et al. documented successful impact of the 2004 AAP Practice Guideline on NICU re-admissions within 28 days of birth for extreme hyperbilirubinaemia (TSB more than $428 \mu\text{mol/l}$) or the use of exchange transfusion (11).

The recommendation includes an algorithm for the commencement of phototherapy based on the value of TSB as well as gestational age, postnatal age in hours, and individual risk factors. Obviously, contraindications of phototherapy exist, predominantly the anamnesis of congenital erythropoietic porphyria or family history of porphyria. During phototherapy it is better to avoid treatment by certain photosensitive drugs such as non-steroid antiflogistics (ibuprofen), diuretics (furosemide, hydrochlorothiazide), some antibiotics (ciprofloxacin, ofloxacin, levofloxacin). In general, photosensitivity with certain medications occurs more commonly during the exposure to the ultraviolet light. As phototherapy (PT) does not produce significant amount of UV radiation, phototoxic reactions in newborn infants with above mentioned medical treatment are rare (12).

In diagnostics of neonatal jaundice an alternative method to estimate serum bilirubin level is measuring the bilirubin transcutaneously. Transcutaneous bilirubinometers measure yellow coloration of the skin and subcutaneous tissues and this information convert to estimated TSB (13).

Transcutaneous bilirubinometry reduces the likelihood of overlook clinically significant hyperbilirubinaemia and simultaneously reduces the number of blood tests (14). Authors Časnocha-Lúčanová et al. tested the accuracy of transcutaneous bilirubin (TcB) measure in newborns undergoing phototherapy. They measured the total serum bilirubin and TcB concentration 2 hours after discontinuing phototherapy. They reported that TcB consistently underestimated TSB levels significantly. TcB measurements performed 2 h after stopping phototherapy were not reliable, even if they were carried out on the unexposed body area (15).

LIGHT SOURCES USED IN PHOTOTHERAPY

Various phototherapeutic systems are used for phototherapy worldwide. Currently two types of phototherapeutic systems are at disposal: conventional phototherapy and fiberoptic phototherapy. Fluorescent tubes with wider emission spectrum or light emitting diodes (LEDs) with more narrow emission spectrum serve as light sources.

Systems for conventional phototherapy

Devices for conventional phototherapy use fluorescent tubes, halogen bulbs, or light emitting diodes (LED) as light sources. Fluorescent tubes are the most commonly used light sources. They are preferred from the financial point of view. However, the intensity of the light gradually declines and it is, therefore, necessary to change the tubes every 1,000–1,500 hours. Gradual decrease of the radiance intensity has not been proven for halogen bulbs but these are fragile and even more fragile if heated.

LED is a special type of semiconductor diode which emits light when connected to an electrical circuit. Devices usually contain indium or gallium nitrate as a semiconductor. Such a light source can emit highly intensive light and concurrently generate a minimum amount of heat, which allows placing the source closer to the infant (distance at conventional PT 40–50 cm versus 20 cm with LED lamp) and increase the spectral irradiance (16).

LED phototherapy is, therefore, preferred at most neonatology departments nowadays. Another advantage is the absence of the undesired “flickering phenomenon” associated with nausea and dizziness in medical staff. Despite this fact no statistically significant differences in the effectivity of PT using blue-green LED light, blue LED light, or conventional halogen bulbs have been proven. In a recent meta-analysis including 6 randomized controlled trials and 511 full term and late preterm newborns in total no significant difference has been noted in the reduction of TSB with the use of LED in comparison to other types of phototherapy devices (17, 18).

Systems for fiberoptic phototherapy

These devices use a standard light source, usually a halogen bulb. The light from the bulb passes through fiberoptic bundle and gets into a pad of coiled optic fibers. The pad can be

placed in proximity of the skin of newborns and, thus, it is possible to treat infants close to their parents without the need to separate infants from mothers. Furthermore, it allows to avoid complications caused by shading the eyes, such as retinal damage, irritation of eyes, corneal abrasion, or conjunctivitis, as the light from optic fibers is aimed directly to the infant's trunk. Thus, fiberoptic PT is a safe alternative to the conventional PT despite its lower spectral irradiance. For this reason its use is not advisable in serious cases with the need for intensive phototherapy (19).

IMPACT OF PHOTOTHERAPY ON SOME PHYSIOLOGICAL FUNCTIONS IN NEWBORNS

Interference with maternal – infant interaction

During phototherapy newborns are frequently separated from mothers, which can negatively influence the establishment of mother – child bond. Except the cases of serious hyperbilirubinaemia the phototherapy process should, therefore, be regularly interrupted in order to secure breast-feeding, contact of mother with newborn, skin-to-skin contact for proper establishment of parent – child bond (20).

Imbalance of thermal environment and increased water loss

The conventional phototherapy affects the body temperature of newborns, which leads to higher loss of fluids and potential dehydration. More frequent stools can also contribute to the water loss. For this reason thorough monitoring of central body temperature is essential and also appropriate fluid intake should be given (especially in VLBW infants) (21). During phototherapy premature newborns have about 20 % increase in transepidermal water loss despite the treatment in double walled crib with sufficiently moistened air. Daily intake of fluids, thus, might be increased by 10–15 ml/kg per day in order to prevent dehydration (22). When compared with breastfeeding the fluids administered intravenously do not affect the reduction of bilirubin level nor duration of phototherapy in full term newborns. Oral feeding is also important for protection of hydration status of infants (23).

LED phototherapy with low irradiance does not cause significant hyperthermia similar to the conventional PT with the use of blue fluorescent light. However, LED PT with high irradiances (60–120 $\mu\text{W}/\text{cm}^2/\text{nm}$) significantly increases body temperature in icteric neonates in comparison to newborns treated by conventional phototherapy with the use of fluorescent lamps (10–15 $\mu\text{W}/\text{cm}^2/\text{nm}$) or with the use of LED lamp (26–60 $\mu\text{W}/\text{cm}^2/\text{nm}$). Therefore, the increase of body temperature is a function of increase in spectral irradiance intensity rather than the type of light source (24).

Hypocalcaemia

Phototherapy may lead to decreased total and ionized calcium concentrations, especially during the phototherapy of premature babies. Hypocalcaemia is likely to be caused by the increased excretion of calcium in urine. Moreover, light can affect the homeostasis of calcium by the inhibition of the secretion of melatonin in glandula pinealis, thus leading to hypocalcaemia (25). Clinically, hypocalcaemia manifests rarely in connection with phototherapy and, in the vast majority of cases, the calcium level returns to normal within 24 hours after termination of phototherapy (26).

Circadian rhythm disorders

Circadian pacemaker of mammals is located in suprachiasmatic nucleus of anterior hypothalamus. The regulation of circadian rhythm is associated with 12 genes at minimum. For instance Cry 1 gene is a negative regulator while Bmal 1 is a positive regulator. Chen et al. (27) studied the effect of phototherapy on the expression of circadian genes in mononuclears of peripheral blood of icteric infants. The study discovered that phototherapy significantly increased the expression of Cry 1 gene and concurrently decreased the plasmatic

concentration of melatonin leading to the alteration of normal circadian rhythm of newborns and to their abnormal behaviour shown by excessive crying and jitteriness.

The function of melatonin in the regulation of circadian rhythm is being intensively studied. Circulating melatonin comes mostly from glandula pinealis but it is partially formed also in other tissues, e.g. gastrointestinal tract, retina, salivary glands. Its synthesis and secretion are influenced by exposure to light and darkness. Specifically, light suppresses and darkness stimulates its production, thus melatonin is also called hormone of darkness. Together with its antioxidation properties melatonin is also known as a biological modulator of mood, sleep, sexual behaviour, and circadian rhythms. Decreased production of melatonin and disorder of melatonin production at night is related to various disorders of CNS. Short-term and long-term consequences of prolonged exposure of a major part of the body to light in a newborn infant are still unknown (28).

Phototherapy and hemodynamic changes

The impact of phototherapy on systemic hemodynamic parameters has been studied for decades by using Doppler ultrasonography. Despite phototherapy is considered to be generally safe it might come with several adverse effects. The adverse effects include mostly hemodynamic changes manifesting as a decrease in cardiac output resulting from blood flow redistribution. Peripheral vasodilation and lowered motor activity lead to a reduction in cardiac output after 30 minutes of phototherapy. It is followed by an activation of autonomic compensatory mechanism via baroreflex, which results in redistribution of blood flow and changes in heart rate (29).

Based on the published studies it is known that phototherapy causes a decrease in cardiac output which returns back to the original level in 12 hours after withdrawal of phototherapy. The cerebral blood flow increases, conversely, renal blood flow is significantly decreased after 2 hours of light exposition (30). As for the effect of phototherapy on renal circulation, the blood flow has been observed to decrease while renal vascular resistance notably increased after the initiation of phototherapy. In healthy children without ventilation support the blood flow velocity and vascular resistance returned to their initial levels after discontinuation of phototherapy, however in children requiring ventilation support the parameters measured by Doppler ultrasonography did not fall back to their baseline (31).

Considering that phototherapy influences blood flow in various tissues, Borensten-Levin et al. (32) have studied the effect of phototherapy on coronary arteries expecting a decrease in blood velocity due to the presence of the steal phenomenon in peripheral circulation. However, no significant coronary blood flow changes were found in healthy newborns undergoing phototherapy.

Pezzati et al. (33) evaluated changes in blood flow in mesenteric circulation after feeding with the use of either conventional or fiberoptic phototherapy. They studied whether fiberoptic phototherapy influenced postprandial increase in gut blood flow in the same way as conventional phototherapy. By Doppler ultrasonography they measured blood flow velocity in the superior mesenteric artery pre- and postprandially in preterm neonates during and after conventional phototherapy as well as fiberoptic phototherapy. In conventional PT they observed a decrease in postprandial blood flow, while with the use of fiberoptic PT the postprandial blood flow distribution was not negatively influenced, making the postprandial blood flow increase significantly higher than in conventional PT. The authors, therefore, prefer the use of fiberoptic systems to conventional phototherapy in the treatment of hyperbilirubinaemia, mainly in preterm newborns, because it does not influence physiological postprandial blood flow redistribution from peripheral circulation into the gut as it happens in conventional PT.

Phototherapy and changes in heart rate

Uhříková et al. (34) studied the effect of hyperbilirubinaemia and phototherapy on the heart rate and the autonomic nervous system (ANS) by comparing newborns with icterus to

a control group of children without hyperbilirubinaemia, postulating that hyperbilirubinaemia itself can influence the cardiovascular system (CVS) via the neurotoxicity of bilirubin and its effects on the ANS. They revealed subtle differences in CVS regulation caused by hyperbilirubinaemia and phototherapy. These variations were detected using a new non-linear method of heart rate variability analysis.

The observed changes indicate that the ANS response expressed through chronotropic cardiac regulation during and after phototherapy is characterized by a shift in sympatho-vagal balance with the prevalence of sympathetic responses and this change persists at least 30 minutes after stopping phototherapy.

Phototherapy and changes in blood pressure

The principal area of phototherapy effect is not only the skin but also the capillary circulation within the subcutaneous tissue. Regional circulation is influenced by the presence of endothelin-1 (ET-1) and nitric oxide (NO). Endothelin-1 is a strong vasoconstrictor and nitric oxide has a potent vasodilating effect. The regulation between NO and ET-1 is modulated by feedback mechanisms. NO production is stimulated after ET-1 binds to its beta-receptor in the endothelium. Conversely, NO inhibits ET-1 from being released. Under physiological conditions their completely opposing effects regulate vascular tone and help to maintain the blood flow. However, in certain pathologies their mutual balance can be disrupted, leading to changes in hemodynamics and consequent serious clinical symptomatology.

Abu Faddan et al. (35) have studied the effects of phototherapy on ET-1 and NO concentrations using the changes in vitals as markers of hemodynamic stability. They discovered that after 24 hours of phototherapy there was a significant increase in NO and ET-1 serum levels, increase in NO-ET-1 ratio and heart rate, and a notable decrease in mean arterial blood pressure in both term and preterm newborns (table 1, 2). There were no significant changes in respiratory rate. The authors assign the above mentioned changes to the possible disequilibrium of NO and ET-1 occurring during phototherapy, which leads to more pronounced and dominant effects of NO. Although it might be irrelevant in clinically stable newborns it can negatively affect neonates with sepsis and impairment of vital functions. Thorough monitoring of vitals should, therefore, be an undisputed part of neonatal care in patients undergoing phototherapy. Based on these results it can be hypothesized that phototherapy induces vasodilation via increased NO production resulting in significant decrease in MABP. The notable heart rate increase is probably a compensatory mechanism following the drop in blood pressure (36).

Tab. 1 Laboratory and vital sign findings in full term newborns (35)

	Before phototherapy	After 24 hours of phototherapy	P-Value
	Mean $\pm$ SD	Mean $\pm$ SD	
HR	137.59 $\pm$ 8.76	140.62 $\pm$ 5.74	0.049*
RR	50.83 $\pm$ 9.97	50.62 $\pm$ 9.21	0.083
MABP	64.76 $\pm$ 3.26	61.86 $\pm$ 3.30	<0.001*
ET (ng/L)	303.68 $\pm$ 59.92	408.20 $\pm$ 75.32	<0.001*
NO (μ mol/L)	103.61 $\pm$ 58.99	186.38 $\pm$ 72.10	<0.001*
NO:ET ratio	0.35 $\pm$ 0.20	0.47 $\pm$ 0.20	0.001*
* = p < 0.05			

Tab. 2 Laboratory and vital sign findings in preterm newborns (35)

	Before phototherapy	After 24 hours of phototherapy	P-Value
	Mean ± SD	Mean ± SD	
HR	152.43 ± 8.04	157.67 ± 8.45	<0.001*
RR	65.10 ± 4.80	63.71 ± 5.95	0.14
MABP	57.57 ± 3.70	54.33 ± 3.58	<0.001*
ET (ng/L)	316.47 ± 55.19	438.24 ± 73.51	<0.001*
NO (µmol/L)	97.67 ± 46.25	188.00 ± 57.89	<0.001*
NO:ET ratio	0.31 ± 0.14	0.44 ± 0.14	0.004*
* = p < 0.05			

Other possible explanation of the increase in heart rate might be the influence of NO on the heart pacemaker, which results in increased heart rate. Some other studies report a positive correlation between the duration of phototherapy and disruption of hemodynamic stability mainly in preterm neonates (37).

The changes in vital functions during phototherapy can serve as markers of hemodynamic stability. Directing blood flow into dermal tissues can also have a positive impact on the effectiveness of phototherapy as more bilirubin is able to migrate into the skin. Similar changes in vital functions have also been observed by other authors who noted significant increase in body temperature and heart rate. As for the changes in blood pressure in full-term newborns a decrease in systemic blood pressure was observed whereas no change was recorded in preterm neonates. The changes in the monitored parameters did not reach a level that could be defined as hypotension, tachycardia, or hyperthermia (38).

CONCLUSION

Bilirubin is a non-enzymatic endogenous antioxidant agent. In low concentrations bilirubin is capable to scavenge reactive oxygen species, mitigate oxidant-induced cellular damage and oxidative stress. Physiological neonatal jaundice is widely accepted as a protective mechanism of newborns against reactive oxygen species during the first days of their lives (39).

The majority of experts believe that treatment of physiological hyperbilirubinaemia in healthy newborns without other complications is not necessary as the bilirubin toxicity is rare in term newborns without hemolysis (40). It, however, remains a fact that there is no established consensus about the exact level of TSB requiring phototherapy, therefore the use of phototherapy greatly varies, mainly in preterm neonates. Considering the difficulty in quantifying the risk of bilirubin-associated brain damage prophylactic phototherapy to prevent bilirubin encephalopathy is still being practiced, which results in a high number of newborns in NICUs undergoing unnecessary treatment.

Despite phototherapy being considered effective and safe even for ELBW newborns, as previously stated, phototherapy does have potential adverse effects. Recently an epidemiologic survey reported a higher risk of childhood cancer by previous phototherapy (41, 42). The current most suitable strategy is to start with phototherapy only in clearly indicated cases and in regard to all its risks and benefits until the official indication guidelines are available (43).

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