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Phototherapy in Neonatal Hyperbilirubinemia: An Overview

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Abstract: The first report on the use of phototherapy for treatment of neonates with jaundice was published more than 20 years ago. Since then, phototherapy has been used extensively in the treatment of neonatal hyperbilirubinemia.

Phototherapy is the use of visible light for the treatment of hyperbilirubinemia in the newborn.There are different types of phototherapy systems in use in recent times.Effectiveness of phototherapy depends on several factors which should be considered while delivering phototherapy to a jaundiced neonate.Effective phototherapy had decreased the need for exchange transfusion.Proper nursing care enhances the effectiveness of phototherapy and minimizes complications.The purpose of this review article is to provide a conceptual review on role of phototherapy in neonatal jaundice, different types of phototherapy systems in use, recent advances, probable side effects of phototherapy.

Keywords: bilirubin, hyperbilirubinemia, jaundice, neonatal intensive care, newborn, phototherapy.

BACKGROUND:

In 1864 the word was first used in German, which in English became ‘bilirubin’. The word bilirubin was derived in 1868, from the latin word “bilis”=bile and “ruber”=red. Bilirubin is a yellowish brown pigment that is derived from the breakdown of heme. It helps coordinate iron into various proteins, like hemoglobulin, myoglobulin, P450 enzymes, etc. It has been found to have anti- oxidant properties and helps in excreting heme from the body.

Jaundice was derived from the latin word “galbinus”, which describes a greenish - yellow colour. This was termed “jaunisse” in Old French, which became jaundice in English. A common misconception is that the word jaundice arises from French word “jaune” which means yellow. Icterus was derived from the Greek word “Ikteros”. This word refers to both the yellow discolouration and a yellow bird. Icterus is the latinized form of the word. It was believed earlier that a person who was jaundiced could be cured if he looked upon the yellow bird by transferring the disease to the yellow bird. Icterus is used interchangeably with jaundice. Both are used to describe the yellowish discolouration of the sclera and the skin due to increased bilirubin levels in blood.

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DESCRIPTION OF NEONATAL HYPERBILIRUBINEMIA BY ANCIENT AUTHORS:

Year	Ancient authors	Description of neonatal hyperbilirubinemia
Earliest references	Babylonian Talmud/Sumerian tablets	"sign of casteless hatred"
1500 BC	Ebers papyrus	Document-"first surviving account of medical remedies"
1500 BC	Issac Asimov	Book-"chronology of Science and Discovery"
1400s	BartholomaeusMetlinger (Chinese Literature)	Book-"Ein regiment der jungen Kinder"
1875	Johannes Orth(German pathologist)	Described the yellowish discolouration of basal ganglia in a jaundiced neonate

Father of modern phototherapy-"Faroese physician Niels Finsen".When natural sunlight was believed to be beneficical in the treatment of several skin disorders, he developed the first artificial light source especially for the treatment of lupusvulgaris.Later on phototherapy was developed and used for the treatment of neonatal jaundice.

INTRODUCTION:

Phototherapy is considered to be the visible light treatment for neonatal jaundice[1]. Sister Jean Ward, the nurse in charge of the Premature Unit at believed in the powers of fresh air and sunshine.But the doctors were not so keen about this belief and practice that time.So Sister ward used to wheel the infants outdoor into the courtyard of hospital on sunny days,and returns them to the ward just before the doctor's rounds.

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One day in 1956, Sister Ward showed the doctors an undressed neonate whose skin was pale except for a triangular area covered by a cloth/sheet that appeared much yellower than the rest of the body which was uncovered and was let exposed to light.

Sister Jean Ward

Subsequently doctors at Rochford Hospital found that the bilirubin levels left sitting under the sunlight had dropped drastically which subsequently led to the idea of PHOTOTHERAPY in the treatment of a jaundiced newborn[2]

The first artificial light based phototherapy unit was discovered by CREMER et al at Rochford Hospital.In 1985 Mc. DONAGH and LIGHTER clarified the "physical and chemical alterations" that occur in this form of therapy[3]

Bilirubin molecules are bound to collagen and lipoproteins in the interstitial space of epidermis[4].Phototherapy which emits light between 400-500nm wavelength,breaks the bonds between bilirubin and collagen,lipoproteins and increases the excretion of bilirubin[5].The decline in skin bilirubin levels is greater than that of serum bilirubin levels[6]

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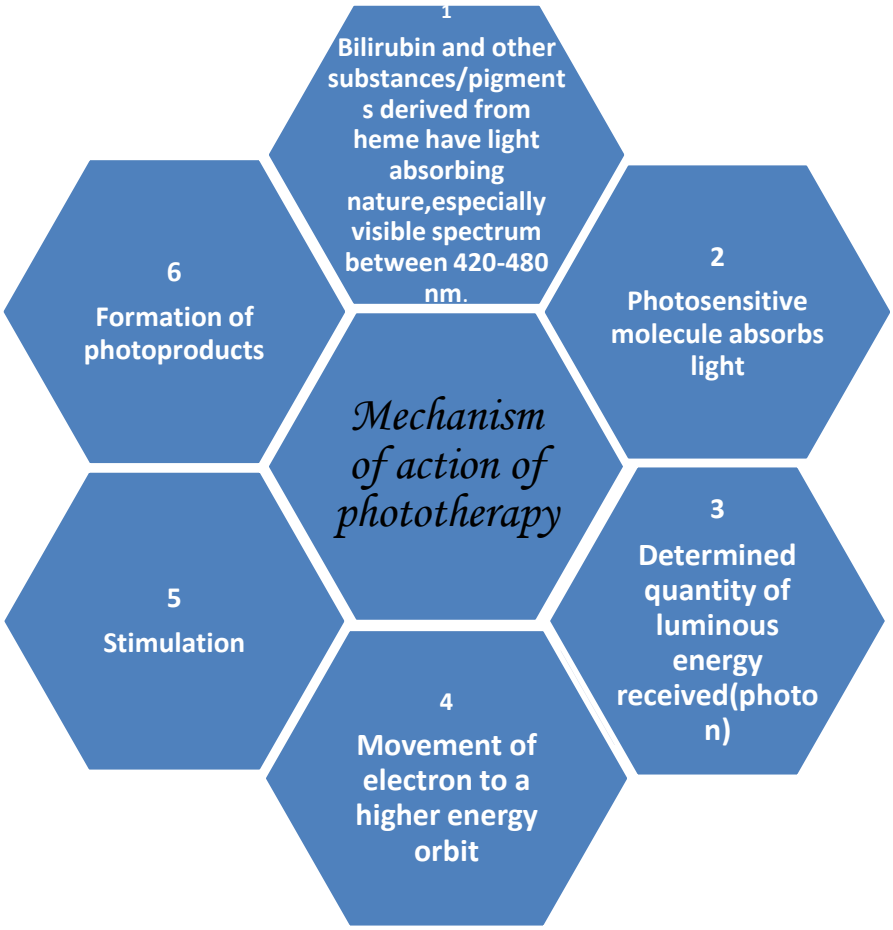
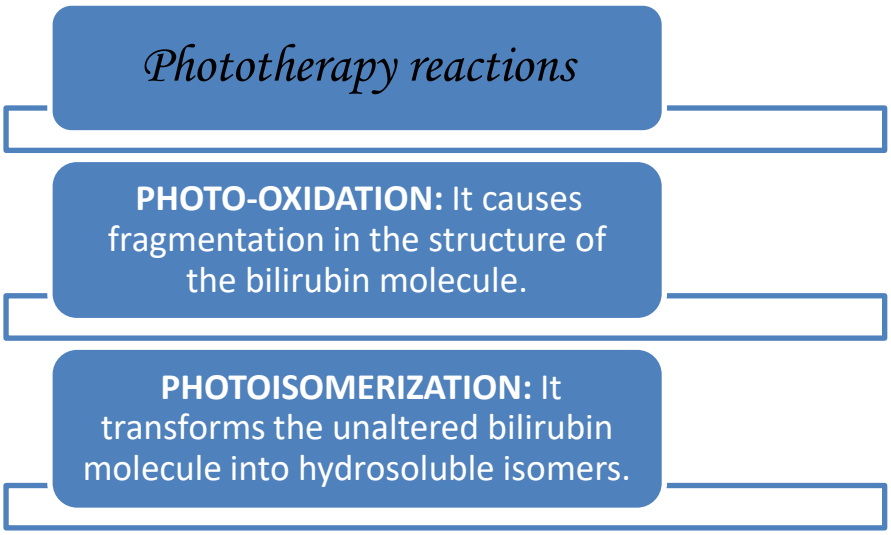
MECHANISM OF ACTION OF PHOTOTHERAPY[7]:





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Bilirubin molecule can undergo 2 types of in vitro photochemical reactions[8]:

- **PHOTO-OXIDATION:**

Absorption of photon by bilirubin molecule

↓

Bilirubin molecule gets stimulated

↓

Envelopes an oxygen molecule

↓

Transformation into free radical

↓

Destruction of native bilirubin

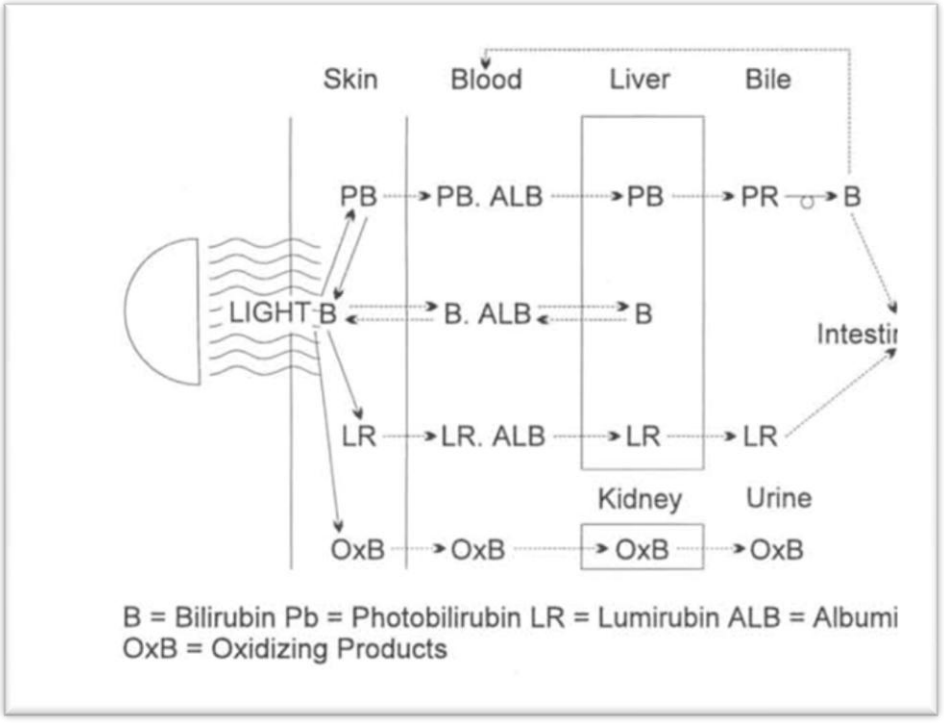
↓

Production of five renal excretion products.

This is a slow reaction and occurs in small quantities.[9]

PHOTOISOMERIZATION: This is a faster reaction.

1) Structural isomer (Iumirubin):It is formed by formation of new bonds between CH-CH2 groups of two adjacent rings involving C2-C7(C=carbons).It is a stable product(slow formation and rapid excretion).So this product doesn't accumulate in the circulation. Hence it is considered as the main efficacy factor of phototherapy.Formation of this isomer depends on luminous intensity.
2) Configuration isomer: Formation of this isomer involves 180^0 rotation of the terminal ring on its axle by which polar segment (NH and COOH)gets exposed to the exterior involving C4 and C15.It has rapid formation and slow excretion, therefore accumulates in the circulation. Its formationdoesn't depend on luminous intensity. This product is unstable and can revert to native form of bilirubin[10,11,12]



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How to measure the EFFICACY of a phototherapy unit?

A phototherapy unit can be considered efficient if it can reduce total bilirubin by 1-2mg/24 hours duration irrespective of other factors[13]The efficacy of a phototherapy unit can be known by quantifying the photoproducts by HPLC[14,15]. The efficacy of a phototherapy depends on several factors:

- numbers of lamps,
- type of light,
- distance from the source,

How to determine the IRRADIATION of a phototherapy unit?

- It is expressed in microwatts mw/ cm2/nm.
- Irradiation of phototherapy is directly proportional to efficacy of phototherapy[16].
- Example: 6 microwatts/cm2/nanometre is low intensity, and that irradiation around 12 microwatts/cm2/nanometreis high intensity(According to several authors)[17,18]
- According to COSTARINO et al. formation of structural isomer Lumirubin depends on irradiation of phototherapy(high intensity phototherapy produces higher quantities of lumirubin) while the formation of configuration isomer doesn't depend on irradiation of phototherapy[19].
- According to MAISELS,increasing irradiation beyond the saturation point(23 mw/cm2/nm) does not raise efficacy[20]
- According to TAN this saturation point should be 40 mw/cm2/nm[21]

Number and type of lamps:

Irradiation of a conventional phototherapy equipment is directly proportional to the number of lamps[22]. Most of the studies recommend the use of Traditional phototherapy equipment which requires 8-12 lamps[23].Recently one light halogen lamps have been used in some services irradiating 23 mw/cm2/nm range which concentrates emitted light in a small and non-uniform area[21].

Time of Use:

White fluorescent lamps show a decline in the irradiance of approximately 25% after 1 hour of use, which decreased to 44% of initial irradiance at 2000 hours of use[24]. However precise data and studies are not available which could conclude the ideal time for the use of phototherapy unit.

Color of the light:

CRAMER described the use of 8 blue 40 W fluorescent lamps[25].It depends on the type of gas used : Iodine, fluoride, neon, tungsten.According to ENNEVER there is no difference between the color of the lamps, and that blue light may not be as good as a conventional white lamp.White light is the most widely employed and the most easily found, seems to be satisfactory, as long as energy emission is kept above 6 mw/cm2/nm.

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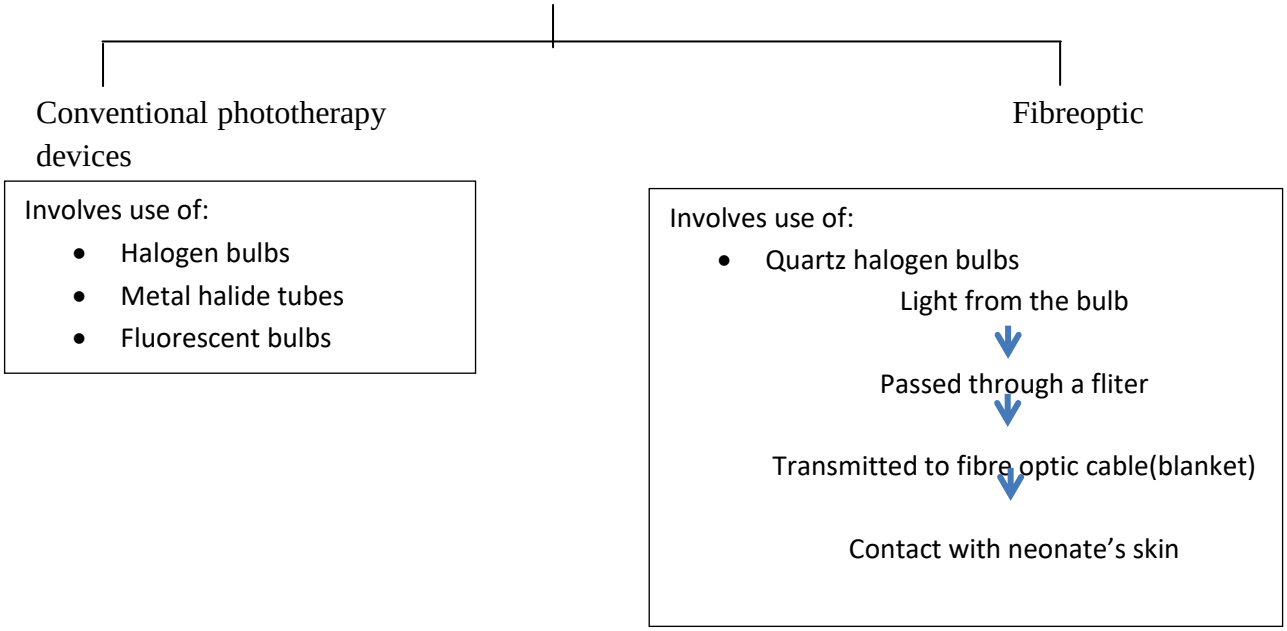
INTERFERENCE FACTORS:

The efficacy of a phototherapy unit can be interfered by several factors which should be given due consideration and appropriate intervention to improve the efficacy of phototherapy[26]:

-Any obstacle between phototherapy unit and exposed area.
-Thermal blankets
-Poor quality of incubator(eg: scratches)

TYPES OF PHOTOTHERAPY SYSTEMS[27]



Phototherapy may be continuous or intermittent.

Continuous phototherapy	Intermittent phototherapy
Without any interruptions	phototherapy for an hour and off for an hour or on for 6 hours and off for 6 hours

Phototherapy may be single surface, double surface or triple surface.

Single phototherapy	Double phototherapy	Triple phototherapy
Use of only 1 phototherapy unit	Use of 2 phototherapy units	Use of 3 phototherapy units

RECENT ADVANCES IN PHOTOTHERAPY IN NEWBORNS:

Novel phototherapy systems are now available and widely in use in some areas which have benefit of increased BSA exposed to phototherapy light and minimal or no interruptance in feeding.

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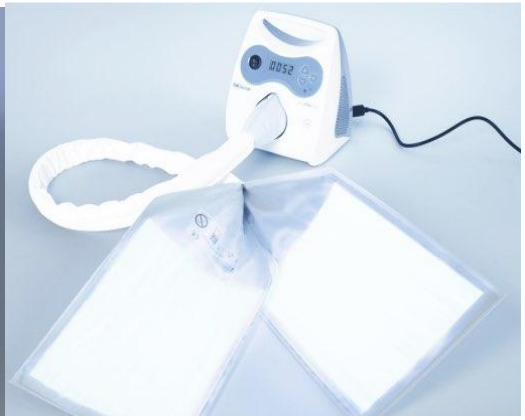
A study was conducted at Hospital Universitario San Ignacio of Bogota,Colombia[28]called "BAG & BLANKET TRIAL" where they have compared the efficacy of bilibags(bilinests) and biliblankets with conventional phototherapy system by a randomised control trial.In blanket trail patients received phototherapy with the latest NeoMed Light Bilicocoon Nest or Ohmedabiliblanket.In bag trial patients received phototherapy with NeoMedblilcocoon bag(sleeping bag with dorsal and ventral light exposure).The parameter under check were serum bilirubin levels(rate of decline),axillary temperature taking into consideration other interference factors.Both bag and blanket groups were then compared with the conventional phototherapy with fluorescent light.On comparison between bag trial group and conventional phototherapy it was found that patients in bag trial have greater proportion of cases with early onset jaundice,But the decrease in serum bilirubin level was found to be similar in both the groups.The difference in body temperature was also clinically insignificant.



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Another study was conducted at NICU,Government Medical college,Kashmir,in which they had compared the efficacy of LED phototherapy with conventional phototherapy[29].The parameters considered were: rate of fall of serum bilirubin levels,duration of phototherapy(Kaplan–Meier analysis) required.They have found that the efficacy of LED phototherapy was more superior to conventional phototherapy considering both the parameters.In addition,patients who received LED phototherapy are at lower risk of reaching threshold for exchange transfusion when compared to those who received conventional phototherapy.

A non-randomized prospective interventional study conducted in a tertiary care hospital of Western India in which they have compared the efficacy of 3 types of phototherapy systems:i) Blue-White Standard Length Tubelight Phototherapy (B&W),ii)CFL phototherapy, and iii)LED phototherapy[30].The parameters considered were mean value of total bilirubin obtained after 24 h of phototherapy,need for exchange transfusion.They have found that mean change in TSB level after 24 hrs of phototherapy was not statistically significant in 3 types of phototherapy systems under study and had stated that more superior trials will be needed to judge the superiority of these 3 types.

NURSING CARE OF AN INFANT UNDER A PHOTOTHERAPY UNIT:

This severely affects the efficacy of phototherapy delivery and efficacy,and ultimately the rate of fall of total serum bilirubin level and length of hospital stay.

- Provide eye protection: This is done with the help of opaque eye patches/eye shields placed on the eyes of infant receiving phototherapy.
- Assess skin exposure: Assessment of area of akin exposed to phototherapy light should be done so as to expose the maximum possible surface area to light.
- Proper positioning :Frequent repositioning of infants toexposure different body areas in not recommended to improve the efficacy of phototherapy.
- Hydration: Several studies proved that increased hydration of infant can shorten the duration of phototherapy.
- Promotion of parent-child interaction : Minimal interruptions of phototherapy is accepted to promote mother-baby interaction,emotional bonding,Kangaroo mother care(skin to skin contact).

SIDE EFFECTS OF PHOTOTHERAPY:

SHORT TERM	LONG TERM
Interferes with mother-baby bonding and interaction	Allergic diseases
Thermal & hydration imbalance	Melanocytic nevi, melanoma and skin cancer
Loose stools	Ocular side effects
Electrolyte disturbances	Patent ductus arteriosus(PDA)
Hypocalcemia	

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Circadian rhythm disturbances	
Bronze baby syndrome	
Riboflavin deficiency	
Bullous eruptions	
DNA damage	
Retinal damage	
Haematological side effects	

These were a few studies in which the side effects of phototherapy were proved to some extent in the selected study population:

Interferes with mother baby bonding and interaction[31]:

Neonatal phototherapy interferes with mother baby bonding and neonatal auditory and visual orientation and alertness.It also increased anxiety in parents.Hence unless jaundice is severe,phototherapy can be interrupted for breastfeeding.

Thermal and hydration imbalance[32]:

Conventional phototherapy may cause insensible water losses,hypothermia/hyperthermia,dehydration,intestinal fluid losses.Hence close monitoring and appropriate fluid supplementation is necessary for maintaining fluid balance and temperature in newborn.

Loose stools[33]:

A study conducted at Department of Paediatrics, Second School of Medicine, University of Naples, Italy in which faecal osmolality and electrolyte concentrations were measured in study groups who received phototherapy and control groups who did not receive phototherapy to find out the cause of diarrhoea in newborns receiving phototherapy.The result showed an increase in intestinal secretion in neonates who received phototherapy for neonatal hyperbilirubinemia which is cause of watery stools. Absorption of water, sodium chloride, and potassium was significantly impaired in the patients receiving phototherapy.But it was found to be a transient effect which was not apparent after stopping phototherapy.

Hypocalcemia[34]:

A cross sectional study was conducted at Koodakan Hospital in Bandar Abbas which aimed to determine the prevalence of hypocalcaemia in the neonates receiving phototherapy. The study groups were divided as neonates <3 days and >days. Serum calcium levels were sent before the start of phototherapy and 48 hours after phototherapy., which showed 9% prevalence of hypocalcaemia in those neonates receiving phototherapy. The study also proved that phototherapy does not increase the risk of hypocalcaemia in full term, healthynewborns.Hence there is no need of prophylactic calcium in such newborns.

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Circadian rhythm disturbances[35]:

A study conducted by Chen et al proved that phototherapy has an effect on circadian genes in peripheral circulation of mononuclear cells of jaundiced neonates Eg: Cry1 gene increased expression and decreased plasma melatonin leading to frequent crying and jitteriness in newborn. Therefore timing of phototherapy is required to accommodate normal circadian rhythm of newborn.

Bronze baby syndrome[36]:

It is a rare complication that occurs due to a rise in conjugated bilirubin(cholestasis). Cu–protoporphyrin metabolism disturbance and congenital biliary hypoplasia are the predictable causes ofBBS.It may be transient and may disappear if phototherapy is discontinued or may have additional risk of kernicterus.

Riboflavin deficiency:

Many previous studies conclusively reported that riboflavin in body cells is degraded by phototherapy.It occurs due to RBC lysis because of deficiency of glutathione reductase in RBC.Gromischet al[37] proved that 16/21 infants who received phototherapy developed riboflavin deficiency.Amin HJ et al[38]measured flavin adenine mononucleotide saturation of RBC glutathione reductase which proved that all neonates who received phototherapy in the study sample developed riboflavin deficiency.

Bullous eruptions:

It occurs due to porphyrins in peripheral circulation.Paller AS et al [39]studied the relation between the eruption and porphyrin levels and reported that distribution of eruption in light exposed areas and circulating porphyrins suggest that porphyrinemia may be the underlying cause of bullous and purpuric eruption.

DNA damage:

Phototherapy can cause oxidative damage to cell membrane and cause free radical injury to DNA.El Abdin MY et al[40] reported that phototherapy causes increased DNA fragmentation in lymphocytes of peripheral circulation when compared to DNA before the start f phototherapy.Tatli MM et al[41] proved as the duration of phototherapy increased,damage to the DNA is also significantly increased by alkaline comet assays.

Thrombocytopenia[42]:

A prospective study was conducted at a tertiary care hospital.The study included all neonates who required phototherapy as per the protocol of American Academy of Pediatrics.It was found that majority of neonates who received phototherapy had thrombocytopenia especially after 24 hours of phototherapy.There were other similar studies(Maurer et al) in which platelet counts were checked after 48 and 96 hours of phototherapy.Incidentally none of the newborns with thrombocytopenia had signs of bleeding manifestations which later proved

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that thrombocytopenia due to phototherapy is a transient effect and rarely found to be severe enough to cause bleeding.

Phototherapy and decrease in serum globulin levels[43]:

A study was conducted in NICU,Zhongnan Hospital of Wuhan University (Wuhan, China) which aimed to assess/prove one of the side effects of phototherapy in neonates. According to previous studies, phototherapy is associated with some immune disorders of childhood later in life. The reason for the occurrence of these immune disorders is that phototherapy causes a decrease of globulin levels in serum. The main aim of this study was to assess the relation of phototherapy on serum albumin and globulin levels. The study summarized a decline in serum globulin levels in those groups who received phototherapy in which some of them required IVIG infusion, with a minimal or no effect on serum albumin levels.

Melanocytic nevi, melanoma and skin cancer[44]:

Phototherapy can cause damage to nuclear and mitochondrial DNA and can cause free radical damage leading to skin cancer. Previous studies conducted by Matichard E et al postulated that larger nevi >2mm are significantly higher in phototherapy exposed groups when compared to controls who did not receive phototherapy.

Ocular side effects:

There is an increased incidence of Retinopathy of prematurity due to decreased oxidation resistance and increased free radical production. It is also postulated that phototherapy causes increased risk of Uveal melanoma due to higher penetrance of blue light compared to UV light when baby's eyes were not covered with an eye patch.

Patent ductus arteriosus(PDA)[45]:
Absorption of photons by cardiac cells
Relaxation of aortic smooth muscle cells via nitric oxide system
Decreased mean arterial pressure
Increased peripheral blood flow

All these mechanisms cause ductus arteriosus to relax and keep open.

Guo Sheng Liu et al proved that phototherapy caused and increase in blood endothelin levels after 24 hours of phototherapy and increased NO levels after 12 and 24 hours of start ofphototherapy when compared to pre-treatment values which ultimately resulted in relaxation of aortic smooth muscle and patent ductus arteriosus.

Taksandeet. al. reported on Phototherapy on cardiac function in neonates with hyperbilirubinemia[46]. Few of the related studies werereviewed[47-50].

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CONCLUSION:

Phototherapy is a safe and inexpensive modality of treatment for neonatal jaundice.It has become the mainstay of treatment of neonatal jaundice.It is highly necessary for all the health centres to evaluate the efficacy and quality of their phototherapy units for acquiring maximum possible benefit and outcome.

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