

“Is there any effect of Phototherapy on Cardiac Function in Neonates with Hyperbilirubinemia”

1]Dr. Amar Taksande, 2] Dr. Jayant Vagha, 3] A. Rupesh Rao.

1] Professor, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha. Email: amar.taksande@gmail.com,9822369233.

2] Professor, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha. Email: jayantvagha@gmail.com,9890625338

3] Junior Resident, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, Email: rupeshrao38@gmail.com,9505152503

Abstract: *Background-* Neonatal jaundice is commonly seen in preterm new born and phototherapy treatment of choice when indicate. Phototherapy is an efficient treatment although there is some side effect present. These side effect may be on behavioural and physiological in some organ and there is also changes in stages of sleep cycle and circadian rhythm during and after phototherapy for few days. These changes in sleep cycle due to the neurotransmitter tryptophan and there is also changes is hormones like decreased in the growth hormones and there is changes in the melatonin which may affect with sleep cycle. there is some study done which suggestive that phototherapy will affect the stages of sleep but there is solid information available whether there is any effect of phototherapy on cardiorespiratory activity. Some old study is suggestive of there is increased in heart rate and decreased in the SBP systolic blood pressure during phototherapy. Phototherapy cause to increase the respiratory rate and heart rate during phototherapy. **Objectives:** To determine the outcome of phototherapy after 24hrs, 48hrs, 72hrs, and >72hrs on cardiac function in term neonates with hyperbilirubinemia. **Results-** After completion of the study we will come to know the effect of phototherapy on cardiac function and also get the idea for how many hours (<24hrs / 48hrs. 72hrs or > 72hrs) we can give safe phototherapy to the neonate with hyperbilirubinemia without affecting the cardiac function. Or is there any need for cardiac shielding during phototherapy. **Conclusion-** After completion of the study we will come to know the effect of phototherapy on cardiac function in term neonate who is having neonatal hyperbilirubinemia.

Keywords- Phototherapy on Cardiac Function, Hyperbilirubinemia

INTRODUCTION

Neonatal jaundice is commonly seen in preterm newborn and phototherapy treatment of choice when indicate. Phototherapy is an efficient treatment although there is some side effect present. These side effect may be on behavioral and physiological in some organ and there is also changes in stages of sleep cycle and circadian rhythm during and after phototherapy for few days. These changes in sleep cycle due to the neurotransmitter tryptophan and there is also changes is hormones like decreased in the growth hormones and there is changes in the melatonin which may affect with sleep cycle.it is reported that melatonin production is started from birth and its production is increased by decreased in

light which was done by covering of eye during phototherapy time (1-5). There is some study done which suggestive that phototherapy will affect the stages of sleep but there is solid information available whether there is any effect of phototherapy on cardiorespiratory activity. Some old study is suggestive of there is increased in heart rate and decreased in the SBP systolic blood pressure during phototherapy(3-10). Many study shows that there is increased in respiratory rate while giving phototherapy during active and sleep where as other study shows that there is increased in respiratory rate during quiet sleep (9-10). It is observed that there is effect of phototherapy on the cardiorespiratory activity but there are many things that is still unclear so for that we are doing tissue doppler echocardiography before and after giving phototherapy to neonate who have hyperbilirubinemia(11).

RATIONALE:

We are using Phototherapy for treatment of neonatal jaundice since many year but it's mechanism of action is properly understand in last 10 year. There are some study which suggestive of that there is increased in peripheral circulation, decreased in systolic blood pressure and increased in respiratory and heart rate while giving phototherapy.so it appeared that there is some effect of phototherapy on cardiorespiratory activity. The rational of these study is to find the effect of phototherapy on cardiac activity in neonate with hyperbilirubinemia.

Research question: Does phototherapy affect cardiac function in neonates with hyperbilirubinemia?

AIMS & OBJECTIVES

Aims: To determine the role of phototherapy on cardiac function in term neonates with hyperbilirubinemia.

Objective:

1. To determine the systolic function before and after giving phototherapy in term neonates with raised bilirubin.
2. To determine the effect of phototherapy after 24hrs, 48hrs, 72hrs, and >72hrs on cardiac function in term neonates with raised bilirubin.
3. To determine the diastolic function before and after giving phototherapy in term neonates with raised bilirubin.
4. To estimate the Cardiac Troponin-T level before and after giving phototherapy in term neonates with raised bilirubin.

MATERIALS AND METHODS

a. Study Setting

This study will be conducted in the Neonatology unit, "Department of Pediatrics, in Jawaharlal Nehru Medical College & AVBR Hospital, Sawangi, Wardha".

b. Sources of Data

Study members: All members in this study will be full-term and appropriate for gestational age newborns with hyperbilirubinemia who will be receiving phototherapy for jaundice (bilirubin level more than 15 mg/dL), according to the AAP (12-14).

c. Inclusion & Exclusion Criteria

Inclusion criteria

- Healthy full-term (gestational age, 37–42weeks) newborn
- Birth weight of 2.5kg–3.5kg
- APGAR at birth is 8–10
- The need for phototherapy for hyperbilirubinemia
- Written informed consent given by the parents

Exclusion Criteria

- Newborns after exchange transfusion
- Inborn errors of metabolism(IEM)
- Jaundice in the first 24 hours of life
- Congenital malformation
- Proven sepsis or infection
- Mothers had a history of Diabetes Mellitus

d. Study Design: Cross-Sectional study

e. Time Frame / Duration: 3 year

PICOT

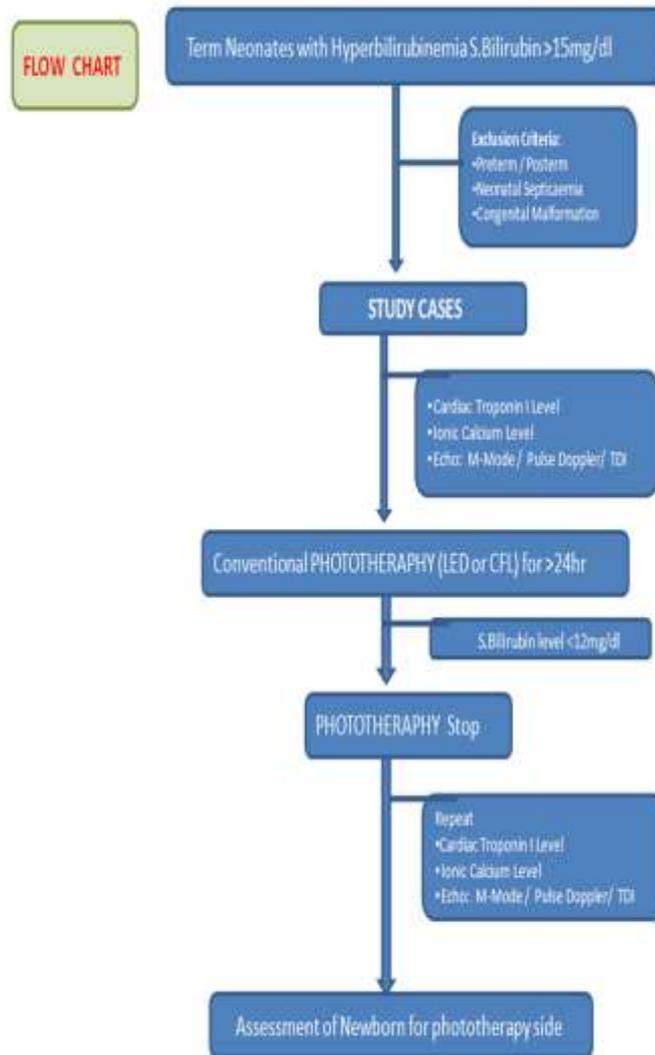
P: Newborn with hyperbilirubinemia

I: Phototherapy

C: ---

O: Cardiac Function

T: Three Year



f. Methodology

A detailed information sheet will be given to the newborn parents in which the methodology of treatment and possible side effects will explain in their local language. Due permission of the ethics committee of the institute will be taken before starting the study.

g. Assessments

Demographic information will be collected for all term neonates with hyperbilirubinemia (study cases), which include age, gender, gestational age(GA), and birth weight. For all study cases, perinatal history and clinical examination done. Laboratory examinations will be included complete blood picture, blood grouping, and Rh typing of the neonate and mother, peripheral smear(ps), and a G6PD test will also be done in all study cases to detect exclusion criteria. Total and direct bilirubin level will be measured by the spectrophotometric method with the Selectra-2 autoanalyzer at the starting of phototherapy, and every 6hrly by transcutaneous bilirubin meter. The phototherapy will be stopped when the total serum bilirubin decreased below 12 mg/dL. Serum Calcium and Cardiac Troponin levels will be done before and after 12 - 24 hours stop of phototherapy.

h. Echocardiography examination

We will be using M mode and 2d echo machine to measure the LV diameter during systole and diastole and also to measure the thickness of IVS during diastole and also thickness of LV posterior wall. We also measure the width of the LA and aorta. The fractional shortening and ejection fraction will be measured by the m-mode and Simpson. We also measure the left ventricular. All the echocardiographic data will be taken as per ASE.

TDI will be performed in the apical 4 chamber view by placing a sample volume at 3 different sites i) Lateral border of MV annulus(LV) ii) IVS and iii) Lateral border of TA (RV). The peak systolic and diastolic velocities at the LV, RV, and IVS will be assessed with TDI in cases and controls. The following parameters will be recorded: systolic velocity (S'), early diastolic velocity (E'), late diastolic velocity (A') and time intervals; isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) and ejection time (ET) at each site. The IVRT will be measured from the end of the S' wave to the onset of the E' wave, and the IVCT will be measured from the end of the A wave to the onset of the S' wave. The formula which will be used to calculate the Tei index is as follow (Isovolemic contraction + isovolumic relaxation time/Ejection time) (15-16).

i. Phototherapy

For treating neonatal unconjugated hyperbilirubinemia Phototherapy remains the mainstay. When a light wavelength of 460-490 nm is exposed to the skin of newborn to treat hyperbilirubinemia it causes the photoisomerization of the bilirubin which was insoluble into the isomers which are soluble that are readily excreted into the bile without any prior need of conjugation and finally excreted in baby's urine and feces. No prophylactic intervention for hyperbilirubinemia will be used. All children were given phototherapy after removing clothes except diapered to allow maximum skin exposure to phototherapy, while environmental lighting will be the same during these studies. using standard phototherapy units Phototherapy will be given by placing 40 cm above the neonate; and it will stop whenever the baby was given for breastfeeding. During treatment, Eye protection will be used, and to achieve uniform exposure to the light neonates will be turned every 6 hours from supine to prone position and vice versa. every six hours newborns Axillary temperature will be measured and infants will be also checked for hyperthermia, rash, dehydration, etc. during phototherapy for possible side effects. (Criteria for dehydration in studied neonates will be low urine output, poor skin turgor and sunken anterior fontanel. Duration of phototherapy is noted in hours.

Ceasing Phototherapy: Phototherapy is continued till serum bilirubin decreased to a safe level i.e. 12 mg/dl by 4th day in term babies. Rebound bilirubin is measured 6-8 hours after stopping phototherapy.

Phototherapy Devices

Many different phototherapy devices are available which use different light source:

- Light-emitting diodes (LED).
- Fluorescent tubes

A good phototherapy device should give a specific blue light of wavelength (peak emission 450 ± 20) and it should cover infant's body surface area of about 80% (1). Irradiance meters for monitoring phototherapy units.

Three main factors which may affect the effectiveness of phototherapy are:

1. **The wavelength of light.**
2. **Lamp energy output (irradiance)**
3. A standard phototherapy lamp was **placed within 40** cm of the patient. when a distance of lamp was increased from the body results in a theoretical decreased in light energy by a factor equal to the square of the increase in the distance. the more the skin is exposed the more is the effectiveness of phototherapy.

Definition

- **Hyperbilirubinemia:** Neonates with serum bilirubin level ≥ 15 mg/dL after 72hours
- **Significant hyperbilirubinemia:** Newborn having serum bilirubin >17 mg/dL after 72hours (1-2)
- **Conventional phototherapy (CPT)** is defined as irradiance of at least 8-10 $\mu\text{W}/\text{cm}^2/\text{nm}$
- **Intensive phototherapy** in which irradiance of ≥ 30 $\mu\text{W}/\text{cm}^2/\text{nm}$ from either a 1 or >1 phototherapy devices is used.

VARIABLES

We will do the following Important VARIABLE earlier and later phototherapy

- Serum bilirubin levels before starting phototherapy and after starting phototherapy
- Serum Calcium level before phototherapy and after phototherapy
- Serum Cardiac Troponin level before phototherapy and after phototherapy
- M Mode (FS & EF for the systolic function of the heart)
- Pulse-Doppler (Diastolic function of the ventricle)
- Tissue Doppler Echocardiography (Myocardial Velocity of the heart)

STATISTICAL TEST

STATA 12 software will be used in analyzing data. Microsoft Excel 2007 will be used for the graph. Numerical data will be summarized using standard deviations and means. The baseline/post-phototherapy measures will be compared using the paired-samples, two-sided *t*-test. Student's *t*-test will be used in Comparison between the two groups with respect to numeric variables for parametric data and for non-parametric data Mann-Whitney test will be used. <0.05 p-values will be considered significant.

SAMPLE SIZE CALCULATION

Single Mean - Paired t-test (By considering: Heart Rate) Reference No. 6

Pre-test mean = 125

Post-test mean = 129

Pre-test Standard deviation= 11

Post-test Standard deviation = 15

Effect size = 0.30769

Power (%) = 90

Alpha Error (%) = 5

Sided = 2

Required sample size = 113

OUTCOME MEASURES

- The primary outcomes will be a difference in cardiac function measured before and after 24 hrs of phototherapy.

- The secondary outcome will be the duration of phototherapy and cardiac function. We will also see the incidence of phototherapy-induced hypocalcemia in our study population and the development of signs and symptoms related to hypocalcemia, such as jitteriness or convulsions.

EXPECTED RESULT-

After completion of the study we will come to know the effect of phototherapy on cardiac function and also get the idea for how many hours (<24hrs / 48hrs. 72hrs or > 72hrs) we can give safe phototherapy to the neonate with hyperbilirubinemia without affecting the cardiac function. Or is there any need for cardiac shielding during phototherapy.

DISCUSSION –

Neonate jaundice is common finding in preterm and term neonates and for treatment of that since long time we are using phototherapy, but in last 10 year we are completely understand the mechanism of action of phototherapy. Phototherapy can affect the different organ system in body and it also effect the hormones in body, because of phototherapy there is change in amount of melatonin production these is due to the changes in the sleep pattern which is due to phototherapy, some study shows that during phototherapy there is increased in heart rate along with decreased in SBP, these is also associated with decreased in respiratory rate.in our study we are doing serum bilirubin during and after the giving phototherapy, and s.calcium before and after calcium, in our study we are using tissue doppler and m mode to know the effect of phototherapy on cardiac function. there is some study which shows changes in the troponin level in baby receiving phototherapy, so we are doing cardiac troponin level before and after the giving phototherapy. During phototherapy there is increased in respiratory rate during sleep.

Walther fj et al(7) did the study by using pulsed doppler echocardiography and evaluated cardiac output and stroke volume in preterm and term neonate.

There is some study which suggested that there is alteration in blood flow to various study during phototherapy Borenstein-Levin et al did study on term healthy neonates who is suffering from neonatal hyperbilirubinemia and treated with phototherapy he found that study group don't show any significant decreased in coronary blood flow velocity, however there is significant increase in peak diastolic velocity, diastolic time velocity integral in left main coronary artery. phototherapy is known to cause increased peripheral blood flow in neonates but information associated with cardiovascular effect is not available.

Walther fj et al(7) did the study using pulse doppler echocardiography and evaluated the cardiac output and stroke volume in term and preterm neonate during and after the phototherapy. They concomitantly measure the arterial limb blood flow by using stain gauge plethysmography and skin blood flow by using photo plethysmography, they reported that cardiac output decreased by 6% due to reduced stroke volume during phototherapy. Whereas the arterial blood flow to limb and skin was increased by 38% and 41% respectively, peripheral blood flow increment tended to higher in preterm then in term neonate. The reduced stroke volume during phototherapy may be due to decreased activity of newborn during phototherapy.

Ed. Uhrikova Z et al (8) study the autonomic nervous effect during phototherapy by observing the heart rate variability during which is controlled by autonomic nervous system. These study show that mean heart rate is increased during and after the phototherapy. The results suggest that there is autonomic nervous system changes during phototherapy in icteric neonates compared to the control.

Bader D et al (10) did the study to assess the cardiorespiratory effect of phototherapy during sleep in term infants with physiologic jaundice. They performed two polysomnography studies during 3 hours sleep in healthy term infants with physiologic jaundice; each infant served as his/her own control. They revealed that there was no difference in sleeping time or the fraction of active and quiet sleep before or during phototherapy. During active sleep under phototherapy there was a significant decrease in respiratory rate and increase in heart rate (54.3 +/- 10.3 vs. 49.1 +/- 10.8 breaths/minute, and 125.9 +/- 11.7 vs. 129.7 +/- 15.3 beats/minute, respectively, $P < 0.05$), as well as a decrease in respiratory effort in response to apnea. These effects were not found during quiet sleep. Phototherapy had no significant effect on oxygen saturation, apnea rate or periodic breathing in either sleep state. Finally, he concluded that phototherapy affected the cardiorespiratory activity during active sleep but not during quiet sleep in term infants with physiologic jaundice.

Gao XY et al (11) conducted the study to clarify whether neonatal jaundice may cause myocardial damage to term infants with normal birth weight (BW). Totally 178 term neonates admitted with normal BW were enrolled. There were no maternal complications during the pregnancy. They found that there were significant correlation between Serum total bilirubin (TB), and cardiac troponin-I (cTnI), MB isoenzymes of creatine kinase (CK-MB), respectively ($r = 0.212, -0.161$, respectively, all $P < 0.05$). But, when the data were analyzed by partial correlation, there was no correlation between TB and cTnI, CK-MB, respectively ($r' = 0.112, -0.112$, respectively, all $P > 0.05$), negative correlation between HR and TB, cTnI, respectively ($r' = -0.490, P = 0.000$; $r' = -0.162, P = 0.032$). There was no significant difference in CK ($Z = -1.384, P = 0.166$), CK-MB ($Z = -0.821, P = 0.412$), cTnI ($Z = -1.159, P = 0.246$), correct Q-T intervals (QTc) ($t = 1.146, P = 0.257$), correct QT intervals dispersion (QTcd) ($t = 1.342, P = 0.185$), left ventricular ejection fraction (EF) ($t = 1.558, P = 0.125$), the ratio of the peak velocity of early stage and advanced stage of diastolic phase at the mitral orifice (E/A) ($t = -0.640, P = 0.525$) between group A and B. There was significant difference in CK-MB/CK ($Z = -3.187, P = 0.001$) between group A and B with a lower value in group A [0.075(0.032 - 0.102)] comparing to that in group B [0.160 (0.073 - 0.284)]. They concluded that there is no sufficient evidence to support the hypothesis that neonatal jaundice may induce myocardial damage in normal birth weight term infants.

Kurhade et al reported on twenty-four hours' transcutaneous bilirubin as a predictor of subsequent 3(rd) day neonatal hyperbilirubinemia(17). Taksande Amar had reported a few rare cases on related to diseases in neonates.

SCOPE OF THE STUDY

- Phototherapy is widely used for the treatment of neonatal jaundice as it is noninvasive, easily available therapy. In term infants It does affect cardiac output and organ blood flow velocity, Also it increases blood flow to the peripheral in neonates, but information on the associated cardiovascular effects is not available.
- Till now, there is not sufficient evidence to see that phototherapy may damage the myocardial in normal term neonate with hyperbilirubinemia, and also there is no study done to see the effect of phototherapy on cardiac function in term neonate who has hyperbilirubinemia.

LIMITATIONS

- Previous studies mentioned that phototherapy may induce hypocalcemia in the newborn with hyperbilirubinemia which may affect the cardiac function of the neonate. To overcome

these problems we will exclude the newborn who develops hypocalcemia after phototherapy.

- Some factors that may lead to neonatal hyperbilirubinemia will not be examined such as spherocytosis, thalassemia, and sickle cell anemia.

IMPLICATION

After completion of the study we will come to know the effect of phototherapy on cardiac function and also get the idea for how many hours (<24hrs / 48hrs. 72hrs or > 72hrs) we can give safe phototherapy to the neonate with hyperbilirubinemia without affecting the cardiac function. Or is there any need for cardiac shielding during phototherapy.

Source of Funding: Institutional funding, DMIMS, Sawangi Meghe, Wardha

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