TPIN Study Protocol

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| **T**hresholds **for P**hototherapy **I**n **N**ewborns  **(TPIN study)** |

**PICO**

Does higher threshold for phototherapy worsen the rate of rise in bilirubin in the first 72 hours of life?

**INTRODUCTION**

**Jaundice**

Jaundice is the most common condition requiring medical attention in newborn babies. About 50% of term and 80% of preterm babies develop jaundice in the first week of life. [1] Jaundice is also a common cause of re-admission to hospital after early discharge of newborn babies. [2] Jaundice usually appears 2 to 4 days after birth and disappears 1 to 2 weeks later, usually without the need for treatment. In most infants with jaundice, there is no underlying disease, and the jaundice is termed physiological. Physiological jaundice typically presents on the second or third day of life, and results from the increased production of bilirubin (owing to increased circulating red cell mass and a shortened red cell lifespan) and the decreased excretion of bilirubin (owing to low concentrations of the hepatocyte binding protein, low activity of glucuronosyl transferase, and increased enterohepatic circulation) that normally occur in newborn babies. In the newborn baby, unconjugated bilirubin can penetrate the blood–brain barrier and is potentially neurotoxic. Acute bilirubin encephalopathy consists of initial lethargy and hypotonia, followed by hypertonia (retrocollis and opisthotonus), irritability, apnoea, and seizures. Kernicterus refers to the yellow staining of the deep nuclei of the brain — namely, the basal ganglia (globus pallidus); however, the term is also used to describe the chronic form of bilirubin encephalopathy, which includes symptoms such as athetoid cerebral palsy, hearing loss, failure of upward gaze, and dental enamel dysplasia.

**Bilirubin Levels indicating neuro-toxicity**

The exact level of bilirubin that is neurotoxic is unclear. It is controversial whether modest elevations of total serum bilirubin (hereafter referred to simply as “bilirubin”) cause brain damage in preterm infants.(3-6) Some observational studies of preterm infants have suggested that bilirubin levels as low as 5 mg per deciliter (86 *μ*mol per liter) or even lower may cause neurodevelopmental deficits.(7-10) However, other

observational studies have suggested that moderately higher bilirubin levels have no neurotoxic effects (11-13) or might even benefit these infants,(14) because bilirubin is an antioxidant.

**Phototherapy**

Phototherapy is considered to be effective and safe in reducing bilirubin levels.(15) However, it has been studied in only one large, randomized trial involving infants treated in the 1970s.(16) No neurodevelopmental benefits were identified,(17) and the findings suggested the possibility that phototherapy might increase the risk of death relative to that among controls in the same birth-weight stratum: for birth weight below 2500 g, the relative risk was 1.32 (95% confidence interval [CI], 0.96 to 1.82); for birth weight below 1000 g, the relative risk was 1.49 (95% CI, 0.93 to 2.40).(18,19) Since that trial was reported, the levels of irradiance delivered by phototherapy lamps have substantially increased, with uncertain effects on the risks and benefits of phototherapy.

**Aggressive vs Conservative PT**

These conflicting data prompted the Neonatal Research Network to perform a prospective randomized

controlled trial in ELBW infants of aggressive phototherapy (used prophylactically and started at 23±9 h after birth) vs conservative phototherapy (started when the TSB level was X8 mg/dl (137 mmol l\_1) for infants 500 to 750 g, or 10 mg dl\_1 (171 mmol \_1) for infants 751 to 1000 g).25 There was no difference in the primary outcome of death or NDI at 18 to 20 months of corrected age but, among survivors, when compared with conservative phototherapy, aggressive phototherapy produced a significant decrease in NDI, hearing loss, profound impairment and athetosis.25 The mean TSB level in infants with hearing loss was 6.5±1.7 mg dl\_1 vs 5.4±1.5 mg dl\_1 (111±29.1 vs 94±25.7 mmol l\_1) in those with no hearing loss (P<0.001). Peak TSB levels in infants with NDI were 8.6±2.3 vs 8.3±2.3 (147±39.3 vs 142±39.3 mmol l\_1, P¼0.02) in unimpaired survivors. Whether these small differences in TSB levels, the use of aggressive phototherapy, or other factors were responsible for the outcomes is difficult to say. An unexpected finding in this study was an increase in mortality in infants with birth weights 501 to 750 g who received aggressive phototherapy (discussed in more detail below), and this must be balanced against the apparent benefit of this therapy. Although, as noted above, survivors in the Neonatal Research Network study who received aggressive phototherapy were less likely to have NDI, there was a 5% increase in mortality in infants with birth weights 501 to 750 g who received aggressive phototherapy25 (relative risk 1.05 (CI 0.90 to 1.22)). The difference was not statistically significant but a post hoc, Bayesian analysis, estimated an 89% probability that aggressive phototherapy increased the rate of deaths in this subgroup. In an earlier NICHD study,17,37 infants with birth weights p1000 g, who received phototherapy, had a 19% increase in mortality compared with control infants (no phototherapy) (P¼0.14). The reasons for these findings are not clear, but these tiny, immature infants have gelatinous, thin skin, through which light will penetrate readily reaching more deeplyinto the subcutaneous tissue. There is some evidence that phototherapy can produce oxidative injury to cell membranes and DNA,38–41 and such injury could have a negative effect on these immature infants. In the Neonatal Research Network study, the average irradiance level was reported as 22 to 23 mW cm2 nm1 and the ‘target irradiance level’ was 15 to 40 mW cm2 nm1.25.

**Current Phototherapy Guidelines**

The 2 major guidelines used by most of NICUs in the world are by (1) UK NICE Guidelines and (2) USA NICHD Network.

UK NICE Guidelines 2016

Treatment threshold graphs for preterm infants remained the same in 2010 and 2016 guidelines. Threshold SBR for phototheray and exchange transfusion are calculated as follows:

Phototherapy

From 72 hrs of age to Day 14 of life: GA at birth x 10 -100 = SBR (umol/L) Threshold

Day 0 to 72 hrs of age: Straight line from 40 umol/L) at 0 hr to 72 hour threshold based on the above calculation.

Exchange Transfusion

From 72 hrs of age to Day 14 of life: GA at birth x 10 = SBR (umol/L) threshold

Day 0 to 72 hrs of age: Straight line from 80 umol/L at 0 hr to 72 hour threshold based on the above calculation.

NICHD Network Recommendations

These GA based recommendations are irrespective of the postnatal age

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| GA at birth | Lowest SBR Threshold (Umol/L) for Phototherapy | Lowest SBR Threshold (Umol/L) for Exchange transfusion |
| <28+0 | 85-102 | 187-238 |
| 28+0 – 29+6 | 102-136 | 204-238 |
| 30+0-31+6 | 136-170 | 221-272 |
| 32+0-33+6 | 170-204 | 255-306 |
| 34+0-35+6 | 204-238 | 289-323 |

**AIM**

1. To study the effect of higher threshold to commence phototherapy in the first 72 hours of life on (1) rate of rise in bilirubin in the first 72 hours, (2) total duration of phototherapy and (3) TSB level reaching 25 umol/L below exchange threshold.

**HYPOTHESES**

**We hypothesise that:**

1. Higher threshold for the commencement of phototherapy will result in similar trends in bilirubin levels in the first 72 hours in comparison to standard threshold group.
2. Total duration of phototherapy and the number of infants reaching TSB levels 25umol/L below Exchange threshold will be similar in both groups.

**OUTCOMES**

**Primary:**

1. Rate of rise in bilirubin the first 72 hours

**Secondary:**

1. Total duration of phototherapy
2. TSB levels at 25umol/L below exchange threshold
3. Plasma sodium>150 mmol/L in the first 3 days of life
4. Weight loss greater than 10% in the first 72 hours of life
5. Clinical outcomes including mortality and significant morbidities (necrotising enterocolitis, sepsis, intraventricular haemorrhage, periventricular leukomalacia, chronic lung disease, retinopathy of prematurity).

**MATERIALS AND METHODS**

1. Prospective observational study of all infants less than 32+0 weeks GA admitted to NICU from 6th March to 6th September 2017.

2. All these infants are regularly monitored for rise in bilirubin levels in the first few days of life as per the routine standard care.

3. Phototherapy will be commenced as per the new guidelines. Subsequent monitoring and management will be done as per the guidelines and standard practice.

4. All the data required for this study are collected routinely as part of clinical care.

5. Infants less than 32 weeks GA and admitted to NICU from 1st January to 31st December will act as historical controls for the study. They would have been managed using the previous phototherapy guidelines. All relevant data for the study will be collected from the case notes and electronic power chart.

**Sample Size**

This is a time specific quality improvement project done as part of independent learning project and the anticipated number of infants during the 6 months of the study would be approximately 60. Similar number of infants for the preceding 6 months in 2016 would act as controls. This gives an approximate total sample size of 120.

**STATISTICAL ANALYSIS**

Statistical analyses will be performed using SPSS (IBM Corp. IBM SPSS Statistics for Windows, version 24.0.0.0. Released 2017. Armonk, NY). Categorical outcome data will be presented as percentages with odds ratio (OR) and 95% confidence interval (CI). Continuous data will be tested for homogeneity of variance using Levene’s test. Non-parametric variables will be compared using either Mann-Whitney U-test.. Parametric variables will be compared using student t test. All p values will be two-sided and the significance level is set at <0.05.

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