

The Effectiveness of Phototherapy in Premature Infants (1968)

In 1968, pediatric researchers Jerold Lucey, Mario Ferreiro, and Jean Hewitt conducted an experimental trial that determined that exposure to light effectively treated jaundice in premature infants. The three researchers published their results in "Prevention of Hyperbilirubinemia of Prematurity by Phototherapy" that same year in *Pediatrics*. Jaundice is the yellowing of the skin and eyes due to the failure of the liver to break down excess bilirubin in the blood, a condition called hyperbilirubinemia. Bilirubin is a product that results from the degradation of red blood cells, which the immature liver of premature infants often has difficulty breaking down. Lucey's group's study demonstrated both the efficacy of phototherapy, which uses light to breakdown the bilirubin in the blood, as treatment for hyperbilirubinemia. As a result of Lucey's research team's study, physicians adopted phototherapy as the standard of care for treating premature infants born with jaundice.

In 1968, the three researchers worked at the University of Vermont College of Medicine in Burlington, Vermont. Lucey was both a physician and a professor of pediatrics at the college and was also the primary researcher of the study. His collaborators on the experiment, Jean Hewitt and Mario Ferreiro, were also faculty members at the University of Vermont College of Medicine who studied pediatrics. At the time, doctors often did not use phototherapy to treat jaundice in premature infants because phototherapy was not widely accepted as an effective method to reduce bilirubin levels. Instead they typically used exchange transfusion, a more complicated procedure that replaced the infant's blood with donor blood to decrease their bilirubin levels.

In 1958, shortly after Lucey joined the faculty of the medical school, Richard Cremer, a physician in England, published his findings regarding phototherapy as a treatment for jaundice in the English journal *The Lancet*. The bilirubin is converted into an intermediate product that is much easier for immature infant livers to excrete.

In 1956, a technician at the Rochford General Hospital in Essex, England, where Cremer worked, observed the effects of light on bilirubin by accident. Instead of taking it to the lab for testing he left a vial of blood that contained high levels of bilirubin in sunlight on a windowsill. When the staff retrieved and tested the vial, they reported that the sample's bilirubin levels had substantially decreased. Cremer based his study around that phenomenon, and he claimed that artificial light likewise decreased the bilirubin levels in jaundiced infants. Cremer's study investigated the effects of light exposure on bilirubin levels in nine premature infants with jaundice. The result of his study supported the claim that phototherapy decreased bilirubin levels, and he published his findings in 1958. Many physicians in the United States, including Lucey, ignored the study because of Cremer's small sample size and his inability to confirm that the results arose due to exposure to light. Other physicians had doubts about the treatment's safety and its effectiveness in treating preterm jaundiced infants.

Lucey and his research team replicated Cremer's experiment but in a controlled, randomized trial on phototherapy and jaundice. Their experiment not only supported Cremer's claims that phototherapy is an effective therapy for treating hyperbilirubinemia, but it also demonstrated that phototherapy could be used as a preventative treatment for that condition. Their findings provided statistical evidence supporting the anecdotal evidence of phototherapy use in over 1,000 infants in the literature at the time of his article's publishing.

Lucey and his colleagues hypothesized that early and prolonged exposure to light prevented or decreased hyperbilirubinemia, eliminating the need for exchange transfusion. The researchers

predicted that levels of bilirubin would decrease in infants who received phototherapy treatment shortly after birth. Their research group consisted of 111 premature infants with jaundice with birth weights of less than 2,500 grams. They placed fifty-three infants in the experimental light treatment group and fifty-eight infants in the control group. To measure the amount of bilirubin in the blood and determine the effectiveness of phototherapy, researchers tested infants' blood samples only on the first, second, fourth, and sixth day of life.

The researchers placed the infants in the experimental group in the light chamber incubator as soon as possible after birth. The incubator contained ten, twenty-watt bulbs, and Lucey's research team exposed the infants to nearly continuous light until they were six days old. Researchers only removed the infants from the incubator for feedings and to take blood samples, which amounted to about one to two hours per day of non-exposure. Researchers did not clothe the infants and repositioned them several times a day to increase the surface area of skin exposed to light. In comparison, they place the infants in the control group in similar incubators for the same amount of time, although those infants remained clothed during the light treatment.

Doctors kept track of changes in the infants' bilirubin levels, and researchers measured the bilirubin levels of the infants in milligrams per 100 ml of blood. If the bilirubin levels of an infant reached twenty milligrams per 100 milliliters of blood, doctors removed them from the study. At that level, bilirubin can become toxic to the infant result in a brain dysfunction called kernicterus, which causes permanent brain damage. For any infant whose bilirubin levels reached above that threshold, doctors removed the infant from the study and immediately treated them with exchange transfusion therapy. However, only one infant had bilirubin levels that required exchange transfusion therapy in Lucey's team's study. For consistency, all infants in the study shared similar birth weights, blood compatibility, and an average gestational age of 35 and 36 weeks so that any change in bilirubin resulted from light phototherapy and not another confounding factor. Each day, nurses tested each infant's blood. By the end of the sixth day, the light-treated group showed lower bilirubin levels compared to the control group. The researchers concluded that phototherapy treatment of premature jaundiced infants was effective without side effects. The researchers concluded that the byproducts from the photochemical breakdown of bilirubin showed no apparent toxicity to the infants.

After concluding the study, Lucey and his colleagues administered a follow-up survey of the health of infants that were a part of the study. The survey found that two infants from the experimental phototherapy group developed motor delays. Previous studies of the impact of bilirubin on infant development had determined that motor delays were common in infants with bilirubin levels above twelve milligrams per 100 milliliters. However, Because the bilirubin levels of the light treatment infants stayed below that threshold, the researchers concluded the developmental delays were not a result to the phototherapy treatment.

The reason for the development of exchange transfusion and phototherapy treatments for jaundiced infants is that high levels of bilirubin can cause permanent brain damage. The longer the high level of bilirubin in the infant's bloodstream persists, the greater the chance hyperbilirubinemia may develop into a brain dysfunction called kernicterus. Lucey and his collaborators noted that when bilirubin levels rapidly rose in infants, phototherapy was ineffective and an exchange transfusion was necessary to reduce bilirubin levels. The researchers also concluded that preterm infants' immature livers and the subsequent impaired bilirubin filtering systems made them great candidates for phototherapy treatment because the slower accumulation of their bilirubin allowed for a greater amount of time for phototherapy to be effective before bilirubin concentration in the blood reached dangerous levels.

When Lucey and colleagues published their study in 1968, scientists questioned what justified an appropriate bilirubin level to begin phototherapy treatment in jaundiced infants. They also questioned whether bilirubin levels actually caused kernicterus. Many experts in the pediatric community questioned the efficacy of phototherapy if bilirubin was not the main factor in an infant's development of kernicterus. Debate continued into the 1970s with Lucey championing the use of phototherapy over exchange transfusion in mild cases of jaundice to prevent the development of hyperbilirubinemia.

In the 1970s and 1980s, literature expanded on phototherapy treatment and hyperbilirubinemia in infants. After Lucey and colleagues' experiment, other researchers conducted similar studies and

treatments of jaundiced infants using phototherapy. Although they were not the first to investigate phototherapy to treat jaundice in newborn infants, Lucey's team's study led to phototherapy being adopted as the standard of care in the United States by the mid-1970s.

Sources

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