Use of a Light Emitting Diode (LED) Array for Bilirubin Phototransformation

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I. Introduction

CONVENTIONAL phototherapy systems rely on fluorescent or halogen light sources, and are therefore limited in their light intensity and portability. Light emitting Diodes (LEDs), which operate at high intensity in the blue region of the visible spectrum, may improve the overall efficacy of neonatal phototherapy, and expand the role of outpatient phototherapy for jaundice.

The newborn liver has a limited ability to process unconjugated bilirubin. Thus, infants are prone to an accumulation of unconjugated bilirubin, and can develop jaundice (hyperbilirubinemia), with serum bilirubin concentrations ranging in severity from minimal, to potentially toxic levels[1]. The goal of medical intervention is to curtail the rise in bilirubin levels and avoid a toxic accumulation. Approximately 10 % of all newborns (including both term and preterm infants) require such intervention[2]. Upon exposure to blue light (410 - 460 nm), a photochemical reaction produces configurational and structural bilirubin isomers which can be excreted directly into the bile or into the urine.

Recently, light emitting diodes (LEDs) which operate in the 410 – 490 nm wavelength range (peak at 475nm) have been developed. These Gallium Nitride(GaN)/Sapphire LEDs can produce high irradience with very low power requirements. These LEDs emit light within the peak absorption range of bilirubin, are low cost, and have long operational lifespans. We hypothesized that an array of light emitting diodes, designed to operate at 410 - 490nm, would phototransform bilirubin more rapidly, in vitro, than either conventional or fiberoptic phototherapy.

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II. Methods

Blue GaN/Sapphire LEDs were assembled, by AMT Inc., into a 4 X 5 array which was electrically coupled in parallel-series. The array was powered by a DC power supply operating at 15.5 Volts and 430 mAmps.

A bilirubin solution (9.03 mg/dl) (Synchron Systems Bilirubin Calibrator, Beckman Coulter) was used as a stock solution for these in vitro experiments. 1 ml of stock solution was placed in a series of 1 ml plastic wells. Up to 16 samples were thus run simultaneously, during any given 4 hour experimental period. The array of samples was kept covered with a 1mm glass plate, thus protecting the samples from contamination, and minimizing evaporative losses. The glass cover plate was transparent to light as measured at 450nm by an Olympic Medical, Olympic Bili-Meter 450 photometer.

There were two groups of controls; the first was exposed to no light (n=16), and the second to ambient room light (n=16). The dark controls were wrapped in aluminum foil and kept in a darkened room during the study period. Ambient light was provided by standard overhead fluorescent lighting approximately 5 feet above the well array. Conventional phototherapy (n=32) was provided by an Ohio Phototherapy Lamp System using two General Electric "Full Spectrum Daylight" bulbs and one Interlectric "BiliBlue" bulb. The light source was situated approximately 47 cm above the surface of the sample wells. Fiberoptic phototherapy (n=30) was provided with a Fiberoptics Medical Corporation, Wallaby II, MD-2000 Phototherapy System. The fiberoptic blanket was positioned directly atop the glass covering the assay wells. For LED phototherapy, the LED array was positioned approximately 1cm above the well array. To assess the effects of light intensity upon bilirubin phototransformation, a total of six samples were illuminated by low irradience LED's, six by six by medium irradience LED's, and twelve by high irradience LED's. Light intensity at the level of the sample wells was measured using an Olympic Medical, 'Olympic Bili-Meter 450' photometer. Total bilirubin concentration was measured at 0, 30, 60,90,120, 180, and 240 minutes, using a Beckman Coulter Synchron Systems Spectrophotometer. Analysis of variance with repeated measures was used to compare the bilirubin values over the four-hour study period, as well as the percent decrease in

bilirubin concentration. Linear regression analysis was used to compare the rates of bilirubin phototransformation.

III. Results

Light intensities emitted by the various systems are shown in Table I.

TABLE I
LIGHT INTENSITIES EMITTED BY THE VARIOUS PHOTOTHERAPY SYSTEMS

Dark Controls	0.0 + 0.0 uW/cm2
Ambient Light Controls	32.0 + 0.0 uW/cm2
Fluorescent Light	420.5 + 1.5 uW/cm2
Wallaby II	259.0 + 19.3 uW/cm2
LED Array	810.8 + 293.4 uW/cm2.

Neither Dark Controls nor Ambient Light Controls exhibited any decrease in unconjugated bilirubin concentration, and were combined for analysis. The bilirubin concentrations over the four hour study period are shown in Table II.

TABLE II
BILIRUBIN CONCENTRATION (MG/DL) AS A FUNCTION OF TIME UNDER PHOTOTHERAPY: A COMPARISON OF PHOTOTHERAPY DEVICES.

Time (min)	Controls	Fluorescent	Wallaby II	LED
0	8.7 + 0.1	8.8 + 0.1	8.8 + 0.1	8.7 + 0.1
30	8.8 + 0.2	8.8 + 0.1	8.7 + 0.2	8.7 + 0.2
60	8.8 + 0.2	8.6 + 0.2	8.5 + 0.1	8.5 + 0.2
90	8.8 + 0.2	8.4 + 0.2	8.4 + 0.1	8.3 + 0.2
120	8.9 + 0.1	8.3 + 0.1	8.2 + 0.1	8.0 + 0.4
180	9.0 + 0.1	8.0 + 0.2	7.8 + 0.2	7.6 + 0.4
240	9.0 +0.1	7.7 +0.2	7.5 +0.2	6.9 +0.6

By 60 minutes, for the fiberoptic and LED groups, and by 90 minutes for the fluorescent group, the bilirubin concentrations were significantly lower than those of controls ($p<0.0001$). All groups were significantly different from one another at 240 minutes ($p<0.0001$). LED phototherapy demonstrated the greatest drop in bilirubin concentration, decreasing it by 20.5 + 6.5 %. Fluorescent phototherapy yielded a drop of 12.4 + 2.2 %, and fiberoptic phototherapy decreased the bilirubin concentration by 14.8 + 2.8 % ($p<0.0001$). Control concentrations increased by 3.0 + 0.2 %. The rates of bilirubin phototransformation (micrograms/dl/minute) were, +1.1 + 0.9 for controls, -4.5 + 0.8 for fluorescent, -5.4 + 1.0 for the fiberoptic, and -7.4 + 2.2 for the LED. By linear regression analysis, phototransformation rates were all significantly different from controls, and significantly different from one another ($p<0.0005$).

The light intensities generated by low, medium, and high power LEDs are shown in table III.

TABLE III
LIGHT INTENSITIES EMITTED BY HIGH, MEDIUM, AND LOW POWER LEDS

Low Power LEDs	411 + 43.9 uW/cm2
Medium PowerLEDs	667.0 + 18.9 uW/cm2
High Power LEDs	1082 + 17.2 uW/cm2

The effects of LED intensity on the bilirubin concentration, over the four hour study period, are shown in Table IV.

TABLE IV
BILIRUBIN CONCENTRATIONS (MG/DL) OVER TIME, AS A FUNCTION OF LIGHT INTENSITY.

Time (min)	Controls	LED (Low)	LED (Med)	LED (High)
0	8.7 + 0.1	8.7 + 0.1	8.7 + 0.1	8.7 + 0.2
30	8.8 + 0.2	8.6 + 0.3	8.6 + 0.2	8.6 + 0.2
60	8.8 + 0.2	8.6 + 0.2	8.5 + 0.1	8.5 + 0.1
90	8.8 + 0.2	8.5 + 0.2	8.3 + 0.1	8.1 + 0.2
120	8.9 + 0.1	8.3 +0.2	8.1 +0.2	7.7 +0.3
180	9.0 + 0.1	8.0 + 0.2	7.7 + 0.3	7.2 + 0.3
240	9.0 +0.1	7.6 + 0.3	6.9 + 0.3	6.5 + 0.5

By 60 minutes, the bilirubin concentrations were significantly lower for all LED groups than those of controls ($p<0.0001$). All groups were significantly different from one another at 240 minutes ($p<0.0001$), with greater drops in bilirubin concentration as light intensity was increased.

The rates of bilirubin phototransformation obtained over the 240 minute period were: for controls 1.1 +0.9 mcg/dl/min, for Low Power LED -4.4+1.0 mcg/dl/min, for Medium Power LEDs -7.3 +1.1 mcg/dl/min, and for High Power LEDs -9.0 +1.5 mcg/dl/min. By linear regression analysis, phototransformation rates were all significantly different from controls, and from each other ($p <0.0005$). The rates of phototransformation were also directly proportional to light intensity ($r = -0.83$, $p < 0.05$).

IV. Discussion

Phototherapy has proven to be an effective treatment for unconjugated hyperbilirubinemia[4]. The success of a phototherapy unit is dependent upon the irradience delivered by the system and the amount of skin exposed to light. Currently, two broad types of light delivery systems are commonly used in the hospital setting. Groups of either fluorescent or halogen bulbs deliver light in the blue region of the spectrum. Their target intensity is based largely upon the maximal blue light output of currently available fluorescent and halogen bulbs. KL Tan reported that a maximal decline in serum bilirubin was achieved at light intensities above 40 uW/cm2/nm of bandwidth [5,6], a value which is over four times greater than current systems provide.

The feasibility of using LEDs as light sources for phototherapy was disclosed previously by Rosen and Rosen in 1997 [7]. In 1998, Vreman, et al, demonstrated the potential of LEDs as a light source for phototherapy, showing that a prototype blue LED phototherapy device generated greater irradience, and faster in vitro bilirubin phototransformation than either conventional phototherapy, white LED, or green LED devices[8]. Seidman, et al, subsequently evaluated a high-intensity GaN blue LED device, demonstrating its greater irradience than conventional phototherapy, but similar average rate of decrease in jaundiced infants[9].

Our phototherapy array utilized LEDs with a different structural design than that used by other authors (8,9), and thus could generate higher light intensity than previous systems. Compared to available conventional systems, the LED phototherapy system generated 71% higher intensity than that achieved with the fluorescent system, and 177% greater than that of the Wallaby II.

Over the 4 hour period, control bilirubin values increased slightly, possibly representing water evaporation from the wells, and thus, concentration of the bilirubin solution over the four hour period. Under phototherapy, all groups exhibited significant drops in bilirubin concentration, likely reflecting the phototransformation of bilirubin. LED phototherapy produced the largest overall drop in bilirubin concentration, and the fastest corresponding phototransformation rate.

Three LED phototherapy light intensities, low, medium, and high, were produced by the array. Under phototherapy, all three LED phototherapy groups exhibited significant drops in bilirubin, and there was a strong direct correlation the between LED light intensity, and the bilirubin phototransformation rate in vitro.

Future work will explore the threshold LED light intensity needed to phototransform bilirubin, and will apply this system to human subjects. The low cost of LED emitters, coupled with their longevity and low power requirements can make LED phototherapy a useful, and possibly a preferred modality for the treatment of neonatal jaundice.

REFERENCES

[1] Woodall DW, Karas JG. A new light on jaundice: a pilot study. Clinical Pediatrics 1992; June:353-356.

[2] Schumann AJ, Karush G. Fiberoptic vs. conventional home phototherapy for neonatal hyperbilirubinemia. Clinical Pediatrics 1992; June:345-352.

[3] Cremer RJ, Perryman PW, Richards DH. Influence of light on the hyperbilirubinemia of infants. Lancet 1958; 1:1094.

[4] Gomella TL, Cunningham MD, Eyal FG. Neonatology: 3rd Edition. New York: Appleton and Lange; 1994. p.316.

[5] Tan KL. The pattern of bilirubin response of phototherapy for neonatal hyperbilirubinemia. Pediatr Res 1977; 90:448-452.

[6] Tan KL. The nature of the dose-response of phototherapy for neonatal hyperbilirubinemia. J Pediatr 1982; 16:670-674.

[7] Rosen D, Rosen A, inventors; Therapeutic Method and Internally Illuminated Garment for the Management Disorders Treatable by Phototherapy. US Patent Number 6,045,575. 2000.

[8] Vreman HJ, Wong RJ, Stevenson DK, Route RK, Reader SD, Fejer MM, et al. Light-emitting diodes: a novel light source for phototherapy. Pediatr Res 1998; Nov:44(5):804-809.

[9] Seidman DS, Moise J, Ergaz Z, Laor A, Vreman HJ, Stevenson DK, et al. A new blue light-emitting phototherapy device: a prospective randomized controlled study. J Pediatr 2000; June:136(6): 771-774.