RESEARCH PAPER

Light-emitting Diodes *versus* Compact Fluorescent Tubes for Phototherapy in Neonatal Jaundice: *A Multi-center Randomized Controlled Trial*

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Objective: To evaluate whether light-emitting diode (LED) phototherapy is as efficacious as compact fluorescent tube (CFT) phototherapy for the treatment of non-hemolytic jaundice in healthy term and late preterm neonates.

Study design: Multi-centre open-label randomized controlled trial.

Setting: Four tertiary care neonatal units. **Subjects:** Healthy term and late preterm neonates with non-hemolytic jaundice.

Intervention: Single-surface LED or CFT phototherapy.

Primary outcome variable: Duration of phototherapy.

Results: A total of 272 neonates were randomized to receive LED (*n*=142) or CFT (*n*=130) phototherapy. The baseline demographic and biochemical variables were similar in the two groups. The median duration of phototherapy (IQR) in the two groups was comparable (26 (22-36) h vs. 25(22-36) h; *P*=0.44). At any time point, a similar proportion of neonates were under phototherapy in the two groups (log-rank test, *P*=0.38). The rate of fall of serum total bilirubin (STB) during phototherapy and the incidence of 'failure of phototherapy' were also not different. An equal proportion of neonates had a rebound increase in STB needing restarting of phototherapy. Side effects were rare, comparable in the two groups and included hypothermia, hyperthermia, rash, skin darkening and dehydration.

Conclusions: LED and CFT phototherapy units were equally efficacious in the management of non-hemolytic hyperbilirubinemia in healthy term and late-preterm neonates.

Key Words: Compact fluorescent tube, Jaundice, Light emitting diode, Neonate, Phototherapy.

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Among hospital born neonates in India, 3% develop serum total bilirubin (STB) levels more than 15 mg/dL(1). Phototherapy is the main treatment for neonatal hyperbilirubinemia. It is most effective in lowering serum bilirubin when wavelength of the light output is in blue to green spectrum (420 to 490 nm)(2). However, there is no standard method of delivering phototherapy. The efficacy of photo-therapy depends on light-source characteristics like emission peak wave-length, emission range and irradiance, apart from various clinical factors(3). The conventional phototherapy units have limited capacity to produce high irradiance and also generate considerable heat. Gallium nitride derived light emitting diodes (LED) which emit high intensity light of narrow wavelength spectrum and produce minimal heat have recently been utilized as light sources in phototherapy units. These units can be placed very close to the neonate without any untoward effects. They are also durable light sources with an average life of 20,000 hours. These unique

Accompanying Editorial: Pages 127-128.

characteristics of LEDs make them an attractive light source for the optimal phototherapy unit. Although LED devices have been shown to be effective in *in vitro* studies, the clinical data comparing LEDs with conventional units is limited(4-9). Hence, we conducted this trial to answer the question "whether LED phototherapy is as efficacious as the standard compact fluorescent tube (CFT) phototherapy in management of healthy term and late preterm neonates with non-hemolytic jaundice".

METHODS

This was an open-label multi-center randomized controlled trial conducted in four tertiary care neonatal units across India, from November 2007 to July 2008. The study protocol was approved by institutional ethics committees of all the four hospitals and the study was registered with Clinical Trial Registry of India. A written informed consent was obtained from one of the parents before enrolment.

Subjects: Newborn infants born at 35 or more completed weeks of gestation were eligible for enrolment, if they developed hyperbilirubinemia needing phototherapy within first 7 days of life. The decision to start phototherapy was made by bedside physicians on the basis of the age of the baby in hours and STB levels, as per American Academy of Pediatrics guidelines(3). Phototherapy was stopped when two consecutive STB levels, measured 6 hours apart were less than 15 mg/dL. Infants with perinatal asphyxia (Apgar score <4 at 1 minute or <7 at 5 minute), onset of jaundice within 24 h of age, evidence of hemolysis (positive direct Coombs test), rhesus hemolytic disease, culture-positive or clinical sepsis, need for exchange transfusion at the time of enrolment, and major congenital malformations were excluded.

Intervention: Enrolled infants were randomized to receive single surface LED or CFT phototherapy. A web-based random number generator was used for block randomization stratified for each center(10). The site investigator allocated the group by opening serially numbered, opaque, sealed, identical envelopes containing the treatment group allocation after obtaining the informed consent. The prototype LED phototherapy units (Srichakra Scientifics, Hyderabad) had multiple LED bulbs arranged in an area of about 20×15 cm. The units were pre-tested by Electronics Regional Test Laboratory (East), Government of India at Kolkata and showed peak emission wavelength between 461 to 467 nm. Commercially available CFT units consisting of 6 special blue compact fluorescent bulbs (18W, OSRAM special blue lamp) were used for the study. Two phototherapy units of each type were designated as 'study machines' at each center and were available for the study cohort. An eligible infant was enrolled only if at least one phototherapy unit of each type was available at the given time. At the beginning of the enrolment, new lamps were installed in all the units. The CFL lamps were replaced during the study period as and when they were visibly discolored or were producing less light or when the irradiance fell to less than 15 $\mu W/cm^2/nm$. The LED lamps were not changed during the study period. In both the groups, each enrolled neonate received phototherapy using a single overhead phototherapy unit. A distance of 25-30 cm was maintained between the baby and the bulb/lamp surface for both type of units. Site investigators were free to provide additional therapy for hyperbilirubinemia like fluid/feed supplementation and phenobarbitone. In all the centers, the study babies were cared for in wards with environmental temperature control. Radiant heaters or blowers were used as and when required.

Outcome variables: The duration of phototherapy was the primary outcome. It was calculated by subtracting age at start of phototherapy from age at end of phototherapy in hours. Brief periods of discontinuation of phototherapy for feeding the baby or changing nappy were not excluded while calculating total duration of phototherapy. The secondary outcomes were failure of phototherapy, rate of fall of STB and occurrence of hypothermia. 'Failure of phototherapy' was defined as STB rising or becoming more than 20 mg/dL during phototherapy, which required either use of double surface phototherapy or exchange transfusion. 'Rate of fall of STB' was calculated by dividing the difference between STB at start and end of phototherapy with duration of phototherapy.

Data collection and monitoring: Clinical

monitoring was done for side effects of phototherapy like dehydration and skin rash; and a 4-hourly axillary temperature measurement was done to detect episodes of hypothermia or hyperthermia. STB was measured every 6 to 8 h using bilirubinometers based on direct spectrophotometery (Twin-beam micro-bilimeter, Ginevri Technologie Biomediche; Italy or Unibeam microbilimeter, Ginevri Technologie Biomediche, Italy; or Bil-100, Cosmo Medical, Korea; coefficient of variation 1 to 3%, range of bilirubin measurement 0-30 to 0-40 mg/dL). Apart from daily internal calibration, the bilirubinometers were checked 3-monthly against low and high bilirubin standards supplied by the respective manufacturers. However, bilirubinometers used at different centers were not compared against each other on the same sample in the same laboratory. In one center (PGIMER,Chandigarh), the irradiance of the phototherapy units at the surface of the babies was checked at the level of face, xiphoid and knees by a photoradiometer (Fluoro-lite 451, Minolta/Air Shields, USA) at the initiation of phototherapy, and then once a day for all babies. In the other 3 centers, only periodic checks of irradiance were done for monitoring and their data was not included for calculating the spectral irradiance.

Sample size: In a previous unpublished trial using CFT phototherapy units in non-hemolytic jaundice, the mean duration of phototherapy was 25.3±14 h. To prove, with 80% power and alpha of 0.05, that duration of phototherapy with LED phototherapy unit is not different by more than 6h, we needed to enroll 125 subjects in each group (Power and Precision software ver 2.0, Biostat Inc., USA).

Statistical analysis: Data entry and analysis were done using Epi Info (CDC, Atlanta). Continuous data with normal distribution was analyzed by student *t*-test and non-normally distributed data by Mann Whitney U test. Categorical data was analyzed by chi-square or Fisher exact test. A *P* value of <0.05 was taken as significant. Analysis was intention-to-treat. It was decided *a priori* that LED will be considered equally efficacious if the difference in duration of phototherapy between the two groups is less than 6 hours without any increase in adverse effects.

RESULTS

The study enrollment is depicted in ***Fig.*1**. The mean birthweight and gestation of enrolled and excluded neonates were comparable. There were 39, 37, 35 and 31 neonates in LED and 39, 35, 34 and 22 neonates in CFT groups at AIIMS New Delhi, FH Hyderabad, PGIMER Chandigarh and CSMMU Lucknow, respectively. There were 9 exceptions to the protocol. Three neonates were enrolled despite low Apgar score (but had no hypoxic ischemic encephalopathy) and six despite the presence of sepsis. The results with and without these cases were comparable and analysis reported here includes these 9 subjects.

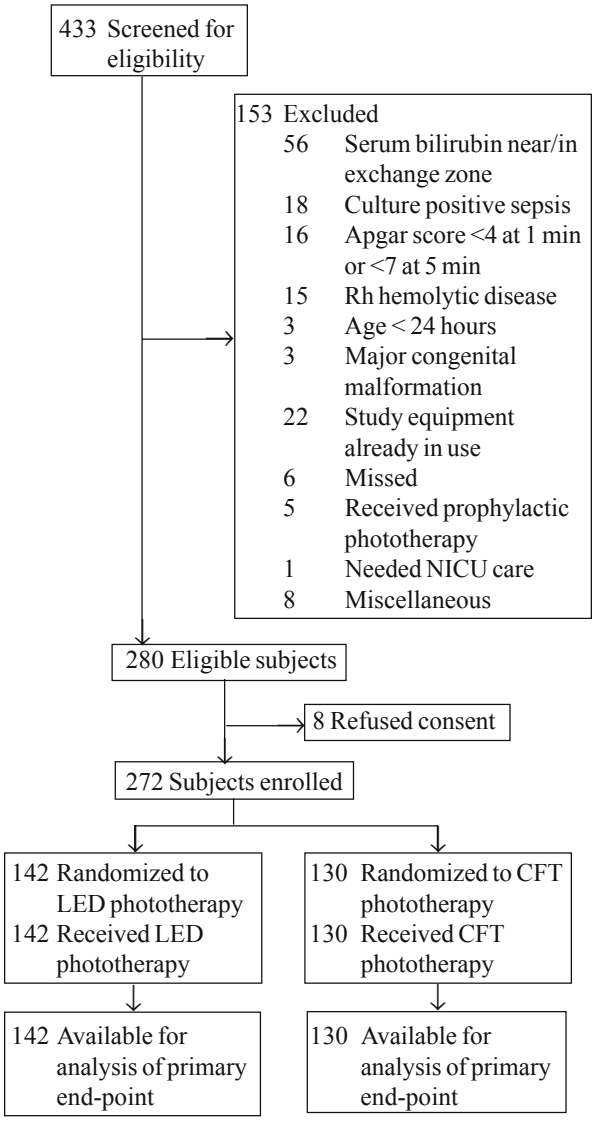

FIG.1 *Trial flow.*

The birthweight, gestation and other demographic variables were similar in the neonates enrolled in LED or CFT groups (***Table* I**). The infant characteristics and laboratory parameters at the start and during phototherapy, which may have impact on the duration of phototherapy were also comparable in the two groups, except for spectral irradiance which was higher in LED group as compared to CFT group (***Table* II**). One neonate in LED group received phenobarbitone while 1 in CFT group received extra intravenous fluids. The STB at the time of stopping phototherapy was similar in the two groups thereby indicating that uniform guidelines were followed.

The duration of phototherapy was normally distributed in the LED group, but was skewed positively in the CFT group (P <0.001; D'Agostino and Balanger test for normality) due to 7 cases in this group needing phototherapy for more than 60 hours (***Fig.* 2**). The median duration of phototherapy was comparable in the two groups [26 h, (IQR: 22-36) versus 25 h, (IQR: 22-36); P=0.44]. At any time point, a similar proportion of neonates were under phototherapy in the two groups (***Fig.* 3**), (log-rank test, P=0.38).

The mean (SD) rates of fall of STB during phototherapy were 0.19 (0.13) and 0.19 (0.14) mg/dL/h in LED and CFT groups respectively (P=0.78). The incidence of 'failure of phototherapy' (6 (4.2%) vs 3 (2.3%); P=0.72) and exchange transfusion (2 (1.4%) vs 0; P=0.50) were similar in the two groups. The subjects with failure of phototherapy were not different from those without failure in terms of age, weight at admission, initial PCV and initial STB. An equal proportion of neonates had a rebound increase in STB needing phototherapy (8 (5.6%) vs 7 (5.4%); P=0.93). Side effects were rare and comparable in the two groups. In the LED group, 3 infants had hypothermia (lowest temperature 36.0°C), 4 developed hyperthermia, 1 had mild dehydration and rash was noticed in 2 infants. Six infants in CFT group developed hyperthermia while skin darkening was seen in one neonate.

TABLE I DESCRIPTION OF STUDY POPULATION

Parameters	LED (n=142)	CFT (n=130)	P
Mean(SD)	n=115	n=110	
Birth weight (g)	2807(458)	2771(489)	0.57
Gestation (wk)	37.6(1.4)	37.6(1.4)	0.88
Median (IQR)	n=128	n=120	
Apgar at 1 min	8(7-9)	8(8-9)	0.42
Apgar at 5 min	9(9-9)	9(9-9)	0.60
Frequency (%)			
Male sex	77 (54)	73 (56)	0.75
Gestational diabetes in mother	10 (7)	10 (8)	0.81
Mode of delivery			
vaginal	86 (61)	80 (61)	0.80#
instrumental	16 (11)	11 (9)	
cesarean	440 (28)	39 (30)	
Setting of ABO incompatibility	53 (37.3)	40 (30.7)	0.26
Rh Negative mother (No isoimmunization)	8 (5.6)	7 (5.4)	0.93
Sibling with jaundice needing treatment	3 (2.9)	6 (6.4)	0.31#
Exclusive breastfeeding	97 (68)	91 (70)	0.75

#*Fischer-exact test* #*Mann-Whitney test*

DISCUSSION

Two hundred and seventy two healthy term and late preterm neonates with non-hemolytic hyperbilirubinemia were randomized to receive LED or CFT phototherapy, across four neonatal units. The efficacy of both types of phototherapy devices in terms of duration of phototherapy, rate of fall of STB, incidence of 'failure of phototherapy' and need for exchange transfusion was similar in this trial.

There is no 'standard' recommended method of administering phototherapy and a variety of strategies have been followed by different researchers. The few earlier publications have compared neoBLUE (Natus Inc., USA) or Super-LED (Fanem, Brazil) devices with either halogen quartz lamps or standard BB blue tubelights(4,6-8). The studies using a strategy of 'similar irradiance' for the two types of devices did not find any difference in their efficacy(4,7,8). Martins, *et al*.(6) adjusted the devices to obtain a similar exposed surface area, but a higher irradiance in the LED group resulted in a better efficacy with LED units.

TABLE II BASELINE VARIABLES WHICH MAY AFFECT DURATION OF PHOTOTHERAPY

Parameters	LED (*n*=142)	CFT (*n*=130)	*P*
Mean (SD)			
Weight at start of phototherapy (*g*)	2644 (434)	2591 (469)	0.32
Age at beginning phototherapy (*h*)	81.7 (35.6)	81.4 (32.5)	0.93
Serum bilirubin at start of phototherapy (mg/dL)	16.8 (2.4)	16.9 (2.5)	0.96
Serum bilirubin at stopping phototherapy (mg/dL)	12.1 (2.1)	12.3 (1.9)	0.65
PCV (%) at start of phototherapy	52.2 (6) in 66	53.1 (6.2) in 56	0.43
Reticulocyte count (%)	2.8 (4.1) in 66	2.0 (2.1) in 55	0.24
Spectral irradiance‡	47 (3.3)	28.7 (2.7)	<0.001
Median (IQR)			
Percent weight loss	4.9(3.1-8.2)in 115	5.8(3.6-8.1) in 110	0.14##
Frequency (%)			
Proportion with weight loss >10%	13 (9.2) in 115	16 (12.3) in 110	0.40
Oxytocin use during labor	59 (42)	65 (50)	0.16
Cephalhematoma	7 (5)	3 (2)	0.34#
G6PD deficient	7/65 (10.8)	3/54 (5.6)	0.35#
Top feed during phototherapy	3 (4.6)	4 (7.1)	0.70#

‡ Based on values obtained in 35 cases in LED and 34 cases in CFT group; #Fischer-exact test ##Mann-Whitney test

We tested an indigenously manufactured prototype LED device and adopted a strategy of 'similar distance' for the two devices. Although, the LED units had a higher spectral irradiance than CFT units, they achieved similar efficacy. In order to explain this, we did a crude estimation of the footprint (body surface area covered) of the two units. The LED unit had a bulb area of 300 cm^2 while the CFT unit had a lamp area of 770 cm^2. The footprint (area in which the irradiance was >15 $\mu W/cm^2/nm$) covered by the two units at the bed level at a distance of 25 cm was 660 cm^2 and 744 cm^2, respectively. Though the CFT unit covered a larger footprint, the lamp area/surface area ratio was 0.96 as against 2.2 for LED unit. The advantage of the higher spectral irradiance achieved with LEDs might have been neutralized by the lesser

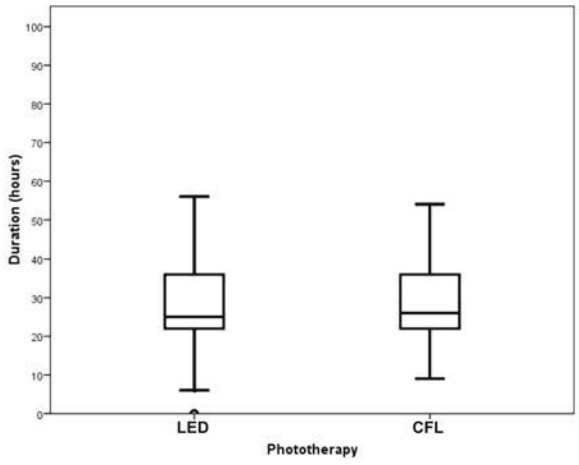

FIG. 2 *Duration of phototherapy.*

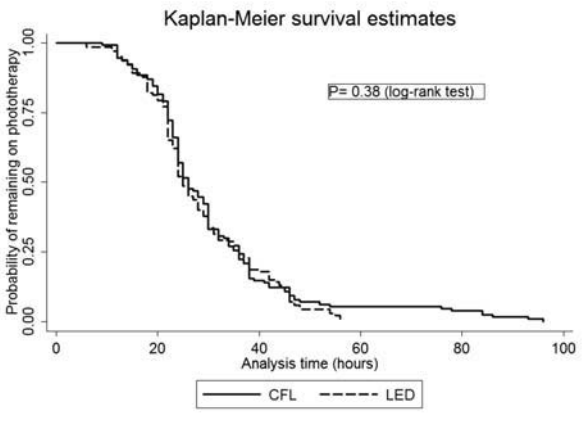

FIG. 3 *Survival analysis: Duration of phototherapy.*

WHAT IS ALREADY KNOWN?

- Light Emitting Diode devices can provide higher irradiance as compared to conventional phototherapy.

WHAT THIS STUDY ADDS ?

- Light Emitting Diode (LED) phototherapy units are at least as efficacious and as safe as Compact Fluorescent Tube (CFT) phototherapy units in healthy term and late-preterm neonates with non-hemolytic jaundice.

surface area covered by these. It is possible that if the bulb area in the LED unit is increased or the arrangement of the bulbs is altered to increase the footprint, its efficacy would improve further. It would be useful to investigate the exact body surface area covered by different phototherapy units in a more scientific manner utilizing irradiance mapping technique(11).

Since we were testing a newly introduced LED system, we enrolled a relatively 'low-risk' population of healthy neonates with non-hemolytic jaundice. Whether LED units will be similarly effective in hemolytic jaundice is not known. The efficacy of a phototherapy system is influenced by initial STB levels, body surface area exposed and spectral irradiance(3). We kept LED light source at a relatively large distance from the body surface to match the distance achievable with CFT photo-therapy. As LED light sources do not produce much infrared light, they can be brought much closer to the baby with potential increase in efficacy, without danger of hyperthermia or burns.

The side effects like hypothermia and hyperthermia were rare and comparable in the two groups. This may be partly because the enrolled neonates were treated in temperature controlled environments with regular monitoring of body temperature. Since LEDs do not produce much heat, hypothermia may be a problem when used in small and sick babies, and in environments without temperature control. In such situations, a closer monitoring and external heat source may be required.

In different centers, STB was measured by three different bilirubinometer models from two manu-facturers. It was not feasible to compare the bilirubinometers used at different centers against each other by running the same sample. However, all centers followed regular internal calibrations and periodic checking against known standards. The irradiance could not be measured regularly at all centers. However, that should not affect the results since a strategy of keeping 'similar distance' for the two devices was being followed rather than 'similar irradiance'.

Although phototherapy has been used for the treatment of neonatal hyperbilirubinemia for more than four decades, the most efficacious method with least side effects is yet to be developed. There is a need to conduct actual cost-effectiveness studies using different phototherapy devices. Studies are also required to compare different types of LED devices. For better comparison, future studies should record not only the distance and irradiance but also the body surface area covered by them. The effects of LEDs on conversion of bilirubin to various bilirubin isomers also needs to be studied *in vitro* and *in vivo*.

Contributors: PK, AKD, GKM, SM and DC designed the study. KN, SS, VS and SNS recruited the subjects and collected the data. PK, AKD, GKM, PG and SM monitored the patient recruitment and data collection. DC and PK analyzed data and wrote the manuscript with inputs from AKD, GKM and SM. All authors reviewed the final manuscript and made the decision to submit the manuscript for publication.

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Conflict of interest: None stated.

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