

# Filtered sunlight versus intensive electric powered phototherapy in moderate-to-severe neonatal hyperbilirubinaemia: a randomised controlled non-inferiority trial

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## Summary

**Background** Kernicterus resulting from severe neonatal hyperbilirubinaemia is a leading cause of preventable deaths and disabilities in low-income and middle-income countries, partly because high-quality intensive phototherapy is unavailable. Previously, we showed that filtered-sunlight phototherapy (FSPT) was efficacious and safe for treatment of mild-to-moderate neonatal hyperbilirubinaemia. We aimed to extend these studies to infants with moderate-to-severe hyperbilirubinaemia.

**Methods** We did a prospective, randomised controlled non-inferiority trial in Ogbomoso, Nigeria—a simulated rural setting. Near-term or term infants aged 14 days or younger who were of 35 weeks or more gestational age and with total serum bilirubin concentrations at or above the recommended age-dependent treatment levels for high-risk neonates were randomly assigned (1:1) to either FSPT or intensive electric phototherapy (IEPT). Randomisation was computer-generated, and neither clinicians nor the parents or guardians of participants were masked to group allocation. FSPT was delivered in a transparent polycarbonate room lined with commercial tinting films that transmitted effective phototherapeutic light, blocked ultraviolet light, and reduced infrared radiation. The primary outcome was efficacy, which was based on assessable treatment days only (ie, those on which at least 4 h of phototherapy was delivered) and defined as a rate of increase in total serum bilirubin concentrations of less than 3.4  $\mu\text{mol/L/h}$  in infants aged 72 h or younger, or a decrease in total serum bilirubin concentrations in those older than 72 h. Safety was defined as no sustained hypothermia, hyperthermia, dehydration, or sunburn and was based on all treatment days. Analysis was by intention to treat with a non-inferiority margin of 10%.

**Findings** Between July 31, 2015, and April 30, 2017, 174 neonates were enrolled and randomly assigned: 87 to FSPT and 87 to IEPT. Neonates in the FSPT group received 215 days of phototherapy, 82 (38%) of which were not assessable. Neonates in the IEPT group received 219 treatment days of phototherapy, 67 (31%) of which were not assessable. Median irradiance was 37.3  $\mu\text{W/cm}^2/\text{nm}$  (IQR 21.4–56.4) in the FSPT group and 50.4  $\mu\text{W/cm}^2/\text{nm}$  (44.5–66.2) in the IEPT group. FSPT was efficacious on 116 (87.2%) of 133 treatment days; IEPT was efficacious on 135 (88.8%) of 152 treatment days (mean difference  $-1.6\%$ , 95% CI  $-9.9$  to  $6.7$ ;  $p=0.8165$ ). Because the CI did not extend below  $-10\%$ , we concluded that FSPT was not inferior to IEPT. Treatment was safe for all neonates.

**Interpretation** FSPT is safe and no less efficacious than IEPT for treatment of moderate-to-severe neonatal hyperbilirubinaemia in near-term and term infants.

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## Introduction

Severe neonatal hyperbilirubinaemia is a leading cause of mortality and disability in many low-income and middle-income countries, including Nigeria.<sup>1</sup> The WHO African Region has the highest rate of severe neonatal hyperbilirubinaemia (667.8 cases per 10 000 livebirths).<sup>2</sup> The WHO South-East Asia Region has the second highest rate (251.3 per 10 000 livebirths), whereas the rate in the WHO Americas Region is only 3.7 per 10 000 livebirths. Several hospital-based studies<sup>3–6</sup> have shown that severe hyperbilirubinaemia contributes substantially to neonatal

morbidity and mortality worldwide. According to two 2017 reports,<sup>7,8</sup> 19.4% and 9.0% of the deaths at two Nigerian facilities were due to jaundice and acute bilirubin encephalopathy, respectively. By contrast, the prevalence of acute bilirubin encephalopathy in Canada is one case per 20 000 livebirths.<sup>2</sup>

Nearly 60 years ago, Sister Ward astutely noted that sunlight decreased visible jaundice. Subsequent studies by Cremer and colleagues<sup>9</sup> led to the development of electric-powered phototherapy devices,<sup>10,11</sup> which remain the standard treatment for hyperbilirubinaemia. Timely and

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See [Comment](#) page e1052

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### Research in context

#### Evidence before the study

We searched PubMed with the medical subject headings “sunlight” and “neonatal jaundice” for articles published in any language before July 31, 2015. Of the 37 papers identified by this search, only four studies specifically discussed FSPT, all of which were our own previous work. Our trial was based on a randomised controlled non-inferiority trial done in Lagos, Nigeria to assess the safety and efficacy of FSPT in mild-to-moderate hyperbilirubinaemia. That trial showed that FSPT was non-inferior to, and as safe as, conventional phototherapy. However, it included only infants with mild-to-moderate disease and was done in an urban location with access to electricity and standard phototherapy devices. Furthermore, the FSPT canopy was vulnerable to adverse weather conditions. An updated search on Aug 11, 2018, identified only one further study, which was done by a Lagos-based group who were former members of our research group.

#### Added value of this study

The present study is the next crucial step towards implementation and upscaling of FSPT by showing efficacy and

safety in infants with moderate-to-severe hyperbilirubinaemia in a setting closely resembling a rural community. Additionally, we upgraded the FSPT canopy to a room with a transparent polycarbonate roof and walls lined with previously tested film, which worked well when ventilation was optimised and improved the longevity of the sun-filtering films and stability in inclement weather. Finally, we showed that efficacy as assessed by the rate of fall of total bilirubin concentrations with FSPT was not inferior to that with intensive electric-powered phototherapy (irradiance level of at least 30  $\mu\text{W}/\text{cm}^2/\text{nm}$ ).

#### Implications of all the available evidence

These findings serve as a baseline for the widespread assessment of FSPT in low-resource rural settings. Challenges that still need to be addressed include: the development of procedures for nursing staff and mothers to safely monitor infant body temperatures without relying on standard thermometers, which are not consistently used or available in rural areas; establishment of which infants cannot be safely treated with daytime FSPT alone; and implementation of a plan to deal with infants who need night-time or rainy-day phototherapy.

effective use of phototherapy has nearly eliminated the need for exchange blood transfusion for infants with severe hyperbilirubinemia as well as decreased the incidence of acute bilirubin encephalopathy in high-income countries.<sup>12,13</sup> However, neonates born in low-income and middle-income settings are not so fortunate, especially those born in rural areas where access to health care is poor.<sup>14,15</sup> Furthermore, health-care facilities are often poorly equipped,<sup>14,15</sup> so even if neonates can access treatment, they often receive ineffective phototherapy, or no treatment because of defective devices or an absence of electricity.<sup>16</sup> Several studies have shown much higher rates of acute bilirubin encephalopathy in infants born outside a hospital setting.<sup>3</sup> Exchange transfusions are regularly done, but often too late to prevent acute bilirubin encephalopathy, death, or life-long disabilities associated with kernicterus.<sup>16</sup> The poor availability of effective phototherapy probably contributes to the high prevalence of acute bilirubin encephalopathy in low-income and middle-income countries.

In previous studies, films that are appropriate for use in filtered-sunlight phototherapy (FSPT) have been identified, and the efficacy and safety of FSPT in mild-to-moderate hyperbilirubinaemia in Nigeria has been shown.<sup>17–19</sup> However, before widespread implementation or upscaling of FSPT, investigation of the efficacy and safety in infants with moderate-to-severe disease is warranted.

We compared the efficacy and safety of FSPT with intensive electric phototherapy (IEPT) in neonates with clinically significant, moderate-to-severe hyperbilirubinaemia in a setting designed to mimic rural areas where this therapy is most needed.

## Methods

### Study design and participants

We did a prospective, randomised controlled non-inferiority trial at Bowen University Teaching Hospital in Ogbomoso, Nigeria, a teaching hospital in a city serving a large rural area, which has an open-lawn area that mimics a village setting. Additionally, staff visited three regular clinics on at least a weekly basis and widely publicised the hospital as a site for assessment and treatment of neonatal jaundice in Ogbomoso and the surrounding areas. Eligible participants were near-term and term neonates aged 14 days or younger who were of 35 weeks or more gestational age (or weighed  $\geq 2.2$  kg if gestational age was unknown) and had total serum bilirubin concentrations at or higher than the postnatal age-dependent treatment concentrations as recommended by the American Academy of Pediatrics for high-risk infants irrespective of actual gestational age.<sup>20</sup> At the discretion of the treating physician, neonates needing exchange transfusions were included if they otherwise met inclusion criteria. Neonates were excluded from the trial if they required referral for treatment of another condition that was not available at the site hospital, were unlikely to survive the first 24 h of life as judged by clinicians, were already clinically dehydrated or sunburned, needed treatment not compatible with FSPT, such as oxygen or intravenous fluids, or if their temperature was not between 36°C–38°C at the beginning of the study.

For this study, we revised our previously published FSPT protocol<sup>21</sup> to include neonates with moderate-to-severe hyperbilirubinaemia admitted during the day and to make other minor changes to comply with the standard of care at Bowen University Teaching Hospital and in more rural areas.

Institutional review boards at Bowen University Teaching Hospital, the Minnesota Medical Research Foundation, and the University of Minnesota approved the protocol. Additionally, the National Health Research Ethics Committee of Nigeria concluded that the study was appropriately reviewed and approved as provided for in the National Code of Health Research Ethics, and the National Agency for Food Administration and Control granted permission to publish the study. Written informed consent was obtained from the parents or guardians of all participants by a trained study nurse.

### Randomisation and masking

Enrolled neonates were assigned (1:1) to receive either FSPT or IEPT via a randomisation procedure with variable block sizes to maximise unpredictability. The randomisation assignments were computer-generated by the study statistician, printed on sequentially numbered sheets of paper, and enclosed in opaque, sealed, sequentially numbered envelopes, which were transported to Nigeria by the regulatory sponsor. When an infant was enrolled by the study nurse, she opened the envelope and the envelope number and treatment assignment were recorded on the case report form. This study was not blinded because we could not mask the neonates, parents, or hospital personnel.

### Procedures

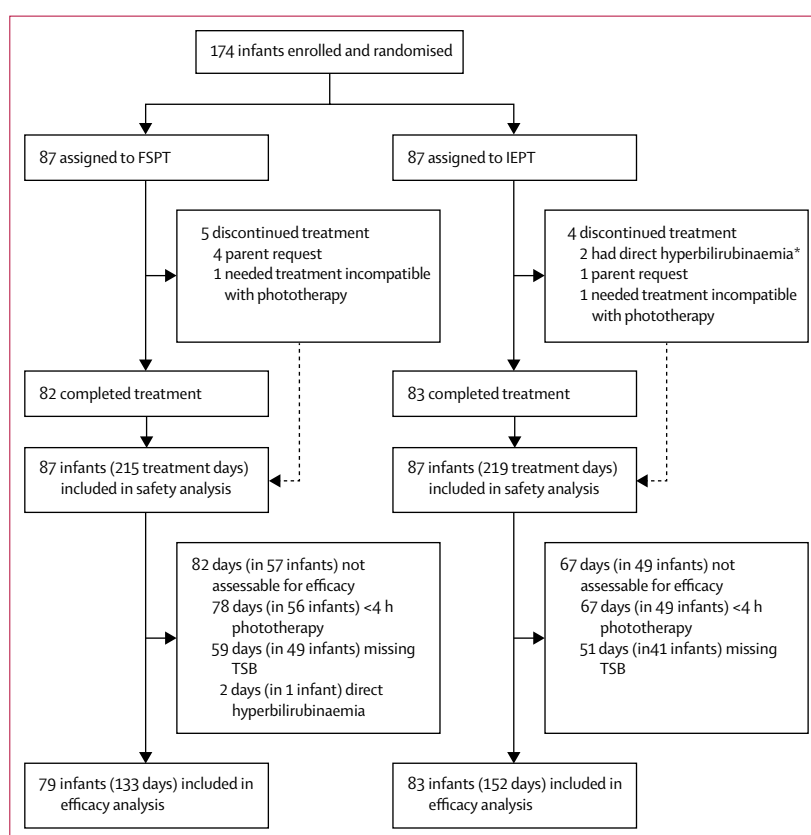
Inborn neonates were screened daily for jaundice at Bowen University Teaching Hospital and at selected clinics on immunisation days when our staff were available. Clinic staff at outlying sites were encouraged to transfer infants with jaundice to the study site for assessment. Additionally, neonates aged 14 days or younger were screened if they presented with jaundice or were noted to be jaundiced by a health-care provider. Total bilirubin concentrations were measured with a transcutaneous bilirubinometer (JM-103, Draeger Medical, Telford, PA, USA) placed on the forehead. If transcutaneous bilirubin concentrations were high according to the 2004 American Academy of Pediatrics guidelines (concentration defined as increased on the basis of day of life for high-risk neonates  $\geq 35$  weeks, irrespective of actual gestational age),<sup>20</sup> total serum bilirubin concentrations were measured with an Advanced BR2 Stat-Analyzer (Advanced Instruments, Norwood, MA, USA). Neonates aged 14 days or younger who were screened were eligible for enrolment at any time that their total serum bilirubin concentration exceeded the American Academy of Pediatrics cutoffs, with modifications as noted previously.

Total serum bilirubin concentrations were measured at enrolment and at the beginning and end of each treatment day. Direct bilirubin and haematocrit were measured near admission (and again if clinically indicated). Concentrations of glucose-6-phosphate dehydrogenase were measured, and maternal and infant

blood types and Rhesus status were ascertained once near admission.

Neonates randomly assigned to FSPT were cared for in an outdoor room constructed with an aluminium frame and transparent polycarbonate walls and roof lined with tinting film (Air Blue 80), which filtered out more than 99% of UVA, UVB, and UVC rays and some infrared (heat) radiation (appendix).<sup>22</sup> The National Agency for Food and Drug Administration and Control previously approved the importation of the window-tinting films for FSPT research in Nigeria.<sup>17</sup> Additionally, the FSPT room was placed on a concrete slab in a grass-covered courtyard to mimic a rural setting and was fitted with solar-powered fans to provide a cooler environment and decrease the risk of hyperthermia. Ambient air temperatures inside and outside the FSPT room were recorded hourly. Neonates in the IEPT group were exposed to an irradiance of at least  $30 \mu\text{W}/\text{cm}^2/\text{nm}$ . IEPT devices (appendix) were locally constructed from aluminium frames and contained

See Online for appendix



**Figure 1: Trial profile**

Two infants in the FSPT group received IEPT on one treatment day, and an infant in the IEPT group received 3 days of FSPT. Treatment days were not assessable for efficacy if the infant received <4 h phototherapy or if either TSB measurement was missing. These issues often occurred on the same day. Furthermore, because most infants received more than 1 day of treatment, the number of infants completely excluded from the efficacy analysis (eight infants in the FSPT and four in the IEPT group) is much lower than the number of treatment days excluded. FSPT=filtered sunlight phototherapy. IEPT=intensive electric phototherapy. TSB=total serum bilirubin. \*Neonates diagnosed with primarily direct hyperbilirubinaemia were excluded because phototherapy is contraindicated in direct hyperbilirubinaemia.

	Total (n=174)	Filtered sunlight phototherapy (n=87)	Intensive electric phototherapy (n=87)
Sex			
Male	108 (62%)	52 (60%)	56 (64%)
Female	64 (37%)	34 (39%)	30 (34%)
Unknown or missing	2 (1%)	1 (1%)	1 (1%)
Gestational age, weeks (n=144)	38 (37–40)	38 (37–39)	38 (37–40)
Birthweight, kg (n=121)	3.2 (2.8–3.5)	3.2 (2.6–3.5)	3.0 (2.9–3.5)
Age at enrolment, h (n=168)	57 (29–112)	47 (27–102)	59 (33–114)
Infant haematocrit, %	46.0 (41.0–50.0)	45.0 (41.0–49.8)	46.0 (41.0–50.0)
Day 1 total serum bilirubin, $\mu\text{mol/L}$ (n=153)	217 (144–274)	195 (137–267)	229 (162–275)
Infant blood type			
A	35 (20%)	16 (18%)	19 (22%)
B	41 (24%)	19 (22%)	22 (25%)
AB	6 (3%)	4 (5%)	2 (2%)
O	81 (47%)	42 (48%)	39 (45%)
Unknown or missing	11 (6%)	6 (7%)	5 (6%)
Maternal blood type			
A	31 (18%)	15 (17%)	16 (18%)
B	27 (16%)	14 (16%)	13 (15%)
AB	5 (3%)	1 (1%)	4 (5%)
O	103 (59%)	52 (60%)	51 (59%)
Unknown or missing	8 (5%)	5 (6%)	3 (3%)
ABO incompatibility			
Negative	126 (72%)	62 (71%)	64 (74%)
Positive	33 (19%)	17 (20%)	16 (18%)
Unknown or missing	15 (9%)	8 (9%)	7 (8%)
Infant rhesus factor			
Negative	5 (3%)	1 (1%)	4 (5%)
Positive	156 (90%)	81 (93%)	75 (86%)
Unknown or missing	13 (8%)	5 (6%)	8 (9%)
Maternal rhesus factor			
Negative	8 (5%)	3 (3%)	5 (6%)
Positive	156 (90%)	79 (91%)	77 (89%)
Unknown or missing	10 (6%)	5 (6%)	5 (6%)
Rhesus incompatibility			
Negative	152 (87%)	78 (90%)	74 (85%)
Positive	4 (2%)	2 (2%)	2 (2%)
Unknown or missing	18 (10%)	7 (8%)	11 (13%)
Infant glucose-6-phosphate dehydrogenase status			
Present	91 (52%)	48 (55%)	43 (49%)
Deficient	57 (33%)	26 (30%)	31 (36%)
Unknown or missing	26 (15%)	13 (15%)	13 (15%)

Data are n (%) or median (IQR).

**Table 1: Baseline characteristics and laboratory parameters for enrolled neonates**

three or five blue light-emitting diode tubes, with nine light-emitting diodes per tube. The prototype was designed and provided by HJV.<sup>23</sup>

Irradiances were measured twice per h in the FSPT group (because irradiance varied), and daily in the IEPT group (which had constant irradiance) with a BiliBlanket II spectrometer (GE Healthcare, Chicago, IL, USA). In both

groups, neonates wore only nappies and cloth eye shields and were placed in cots lined with a white cloth. They were cared for throughout treatment by their mothers and study nurses. Hourly axillary body temperatures (ABTs) were measured. If ABTs were outside the target range (36.0–38.0°C) during phototherapy, monitoring was more frequent. As previously described,<sup>17</sup> moist white towels were placed under infants to treat hyperthermia and prophylactically when ambient temperatures were high (at clinicians' or carers' discretion). Hypothermia was treated with skin-to-skin contact or wrapping in cloth. Neonates were monitored for sunburn and dehydration hourly when under FSPT or IEPT.

A treatment day was defined as when an infant received any phototherapy between 0800 h and 1800 h. Because many neonates from outlying clinics and rural areas arrived too late to receive more than 4 h of phototherapy, we defined a day in which a neonate received at least 4 h of phototherapy to be a minimum assessable treatment day. Neonates in either group who needed night-time phototherapy were placed under IEPT at approximately 1800 h. Night-time phototherapy was given from approximately 1800 h to 0830 h in both groups. On rainy days, infants in either group who needed phototherapy were placed under IEPT. Total serum bilirubin concentrations were measured in all neonates the morning after a treatment day. If infants still needed phototherapy, they received their original treatment allocations.

Neonates were withdrawn from the study if total serum bilirubin concentrations were no longer sufficiently increased as decided by the treating physician; if ABT did not return to between 36.0°C and 38.0°C within 1 h of being removed from FSPT or IEPT because of hypothermia or hyperthermia; at least two readings of ABT less than 35.5°C or greater than 38.5°C a day on more than 2 days (persistent temperature instability); if treatment was needed for dehydration or sunburn; if an intercurrent illness developed that was not compatible with FSPT (eg, need for intravenous fluids or oxygen therapy); if transfer to another hospital was required; if the neonate died; if a parent or guardian requested that their infant be removed from the study; if the investigator thought that the neonate's wellbeing would be compromised by continuing in the study; or if recommended by the institutional review board.

## Outcomes

The primary outcome was the proportion of assessable treatment days (defined as days when the infant received at least 4 h of phototherapy and both initial and final total serum bilirubin measurements were obtained) on which total serum bilirubin increased by less than 3.4  $\mu\text{mol/L/h}$  (for neonates <72 h old) or decreased (for neonates  $\geq 72$  h old).<sup>17</sup> Safety was defined as the proportion of all treatment days on which the neonate did not have to be removed from FSPT or IEPT because of sunburn, dehydration,

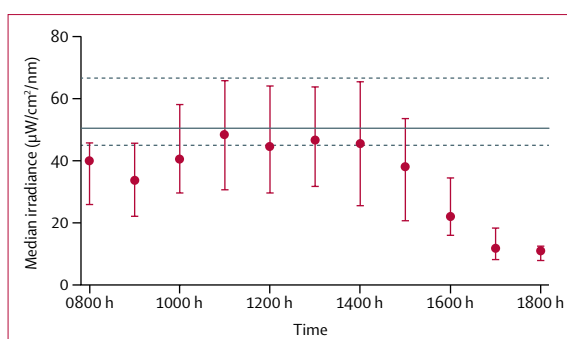
persistent temperature instability, or failure to return to normothermia within 1 h of being removed from FSPT or IEPT. Secondary outcomes were the absolute change in total serum bilirubin concentrations during the treatment day, and the rate of change in total serum bilirubin concentrations in the FSPT group compared with IEPT group.

### Statistical analysis

As used previously,<sup>17</sup> a non-inferiority margin of 10% was chosen for this study on the basis of the clinical investigators' expert opinion. The minimum sample size to show non-inferiority in the efficacy of FSPT compared with IEPT, assuming an average efficacy of 90% for both treatments, a 1:1 allocation ratio, a non-inferiority margin of 10%, and 80% power with a one-sided  $\alpha$  of 2.5%, was estimated to be 284 assessable treatment days. We planned to enrol 198 neonates to obtain 316 treatment days, 284 of which would be assessable for efficacy, assuming 90% assessable treatment days, a typical 2-day treatment course, and up to 20% loss as a result of removal from the trial of neonates by parents or guardians or missing data.

The mean difference in efficacy between the FSPT and IEPT groups was assessed with a normal CI of the difference. Non-inferiority was concluded if the CI did not extend below -10%. The prespecified efficacy analysis was done on an intention-to-treat basis. A post-hoc as-treated efficacy analysis was also done, as was a more conservative per-protocol efficacy analysis, which included only infants who received the assigned treatment on all treatment days. Because the primary analysis was done on the basis of assessable treatment days, not infants, we did a secondary analysis with bootstrap resampling methods to account for potential correlation among treatment days for a given infant. The study data were resampled by infant to preserve correlation structure. The resampling was done with replacement, separately by treatment group, and the efficacy in each treatment group and the efficacy difference were calculated. This procedure was repeated 10 000 times, and the mean and 95% CI were reported. Safety assessments were based on all treatment days on an intention-to-treat basis, as prespecified. Study data were managed with the REDCap electronic database<sup>24</sup> hosted at the University of Minnesota Academic Health Center (Minneapolis, MN, USA).

We used *t* tests, Wilcoxon rank sum tests,  $\chi^2$  tests, Fisher's exact test, or linear regressions for exploratory post-hoc analyses of secondary outcomes and subgroup analyses. We did not adjust for multiple comparisons in the exploratory analyses. Data analyses were done with R (version 3.3.2) running in RStudio (version 1.0.136). The study was overseen by the data safety and monitoring board of the Hennepin County Medical Center (Minneapolis, MN, USA). The study was registered with ClinicalTrials.gov, number NCT02612727.



**Figure 2: Median irradiance by time of day across all enrolled neonates and days**

The irradiance data during the first 50 days of the study were unusually variable, probably because of training issues, and were excluded from this figure. For FSPT, median irradiance is represented by the dots (error bars represent IQR). For IEPT, the solid horizontal line represents the median (dotted horizontal lines represent IQR). FSPT=filtered sunlight phototherapy. IEPT=intensive electric phototherapy.

### Role of the funding source

The study funders had no role in study design or conduct; data collection, analysis, or interpretation; or writing of the report. The corresponding author and senior author (DAG) had full access to all study data and final responsibility for the decision to submit for publication.

### Results

Between July 31, 2015, and April 30, 2017, 174 neonates were enrolled in our trial and randomly assigned: 87 to the FSPT group and 87 to the IEPT group (figure 1). Two neonates in the FSPT group received IEPT on one of their treatment days and a neonate in the IEPT group received 3 days of FSPT. Overall, nine (5%) neonates were withdrawn (figure 1). Baseline characteristics and laboratory test results were well matched between the two groups (table 1). The potential for haemolysis was identified in four (2%) infants as a result of rhesus incompatibility, in 33 (19%) as a result of ABO blood group incompatibility, and in 57 (33%) as a result of glucose-6-phosphate dehydrogenase deficiency (table 1). Direct Coombs testing was not available to diagnose the presence of haemolytic disease secondary to blood group incompatibility.

Overall, neonates in the FSPT group received 215 days of treatment, whereas those in the IEPT group received 219 days of treatment. Enrolment was stopped early when the required number of assessable treatment days was reached. 157 (90%) neonates, 78 in the FSPT group and 79 in the IEPT group, were treated for 2 or more days. The mean number of treatment days did not differ significantly between groups (2.47 days in FSPT group vs 2.52 days in IEPT group;  $p=0.7656$ ). Of the 215 treatment days of FSPT, 82 (38%) were not assessable (figure 1). Of the 219 treatment days of IEPT, 67 (31%) were not assessable (figure 1). Direct hyperbilirubinaemia is a contraindication for phototherapy. Therefore one infant assigned to the FSPT group who was found subsequently



	Filtered sunlight phototherapy	Intensive electric phototherapy
Treatment days received, n	215	219
Assessable days, n (%)	133 (62%)	152 (69%)
Initial (morning) total serum bilirubin (μmol/L)		
Mean (SD)	200 (65)	207 (67)
Median (IQR; range)	193 (147 to 245; 104 to 429)	192 (157 to 255; 103 to 410)
Change in total serum bilirubin (μmol/L)		
Mean (SD)	-18 (34)	-24 (31)
Median (IQR; range)	-17 (-31 to 2; -139 to 70)	-18 (-40 to -5; -145 to 51)
Rate of change in total serum bilirubin (μmol/L/h)		
Mean (SD)	-3.2 (6.2)	-4.1 (5.5)
Median (IQR; range)	-3.1 (-5.8 to 0.3; -30.8 to 12.3)	-3.6 (-7.2 to -1.0; -23.1 to 10.3)
Effective days, n	116	135
Efficacy	87.2%	88.8%
Difference in efficacy (95% CI)	-1.60% (-9.87% to 6.68%)	..
Bootstrap resampling analysis		
Mean efficacy (95% CI)	87.3% (81.3-92.8)	88.8% (83.9 to 93.5)
Difference in efficacy (95% CI)	-1.51% (-9.19 to 6.02)	..

**Table 2: Efficacy of filtered sunlight phototherapy vs intensive electric phototherapy on assessable treatment days in the intention-to-treat analysis**

	Filtered sunlight phototherapy		Intensive electric phototherapy	
	Hourly checks	Infants	Hourly checks	Infants
Infants	..	87	..	87
Periodic checks	1419	..	1538	..
Periodic checks with axillary body temperature	1393 (98%)	..	1520 (99%)	..
Median axillary temperature (IQR), °C	37.1 (36.7-37.4)	..	37.0 (36.6-37.2)	..
Signs of sunburn	0	0	0	0
Signs of dehydration	0	0	0	0
Abnormal axillary body temperature				
Hyperthermia (>38.0°C)				
Any	62 (4%)	33 (38%)	20 (1%)	12 (14%)
Mild (>38.0°C to ≤38.5°C)	48 (3%)	29 (33%)	16 (1%)	12 (14%)
Severe (>38.5°C)	14 (1%)	9 (10%)	4 (<1%)	3 (3%)
Hypothermia (<36.0°C)				
Any	10 (1%)	9 (10%)	24 (2%)	14 (16%)
Mild (≥35.5°C to <36.0°C)	7 (1%)	7 (8.0%)	23 (2%)	14 (16%)
Severe (<35.5°C)	3 (<1%)	3 (3%)	1 (<1%)	1 (1%)
Persistent temperature instability	..	0	..	0
Failure to return to normothermia*	..	≤2 (≤2%)	..	≤4 (≤5%)

Data are n or n (%), unless otherwise specified. The denominator for calculations of percentages is the number of available axillary body temperatures or the number of infants, as appropriate. Differences in proportions of periodic checks by treatment group are statistically significant for overall hyperthermia ( $p<0.0001$ ) and mild hyperthermia ( $p<0.0001$ ), somewhat less significant for severe hyperthermia ( $p=0.0206$ ), overall hypothermia ( $p=0.0467$ ) and mild hypothermia ( $p=0.0119$ ), and not significant for severe hypothermia (Fisher's exact  $p=0.3544$ ). \*Data unavailable for six infants (two in the filtered sunlight phototherapy group, and four in the intensive electric phototherapy group).

**Table 3: Safety of filtered sunlight phototherapy vs intensive electric phototherapy on all treatment days**

to have predominately direct hyperbilirubinaemia was removed from the study after 2 days of treatment. Infants required IEPT at night on 262 (60%) treatment days (126 days in the FSPT group and 136 days in the IEPT

group). A similar proportion in both groups received IEPT at night at least once (73 [84%] infants in the FSPT group vs 76 [87%] in the IEPT group).

Median irradiance was 37.3 μW/cm<sup>2</sup>/nm (IQR 21.4-56.4) in the FSPT group and 50.4 μW/cm<sup>2</sup>/nm (44.5-66.2) in the IEPT group (figure 2).

Pre-treatment TSB concentrations were 200 μmol/L (SD 65; range 104-429) in the FSPT group and 207 μmol/L (67; range 103-410) in the IEPT group (table 2). The mean rate of change in TSB concentrations was -3.2 μmol/L/h (SD 6.2) in the FSPT group and -4.1 μmol/L/h (5.5;  $p=0.254$ ) in the IEPT group. FSPT was efficacious on 116 (87.2%) of 133 treatment days; IEPT was efficacious on 135 (88.8%) of 152 treatment days ( $p=0.8165$ ). The mean difference in efficacy was -1.6% (95% CI -9.9 to 6.7). Because the CI did not extend below -10%, we concluded that FSPT was not inferior to IEPT in terms of efficacy.

The efficacy results of the as-treated and per-protocol analyses were nearly identical to those of the main analysis. On an as-treated basis, FSPT was efficacious on 117 (87.3%) of 134 assessable treatment days and IEPT was efficacious on 134 (88.7%) of 151 assessable treatment days ( $p=0.8507$ ; mean difference in efficacy -1.4% [95% CI -9.7 to 6.8]). On a per-protocol basis, FSPT was efficacious in 116 (87.2%) of 133 assessable treatment days, and IEPT was efficacious on 134 (88.7%) of 151 assessable treatment days (mean difference in efficacy -1.5% [95% CI -9.8 to 6.8];  $p=0.8325$ ). In the post-hoc bootstrap resampling analyses, the mean efficacy was 87.3% in the FSPT group and 88.8% in the IEPT group (mean difference -1.5% [95% CI -9.2 to 6.0]; table 2) in the main analysis. The results were similar in the as-treated (mean difference -1.5% [95% CI -9.0 to 6.0]) and per-protocol (-1.5% [95% CI -9.1 to 5.9]) analyses. There was no evidence of non-inferiority in any of these analyses.

No infant in either treatment group had persistent temperature instability. During the study period, outside ambient temperatures ranged from 25.2°C to 58.2°C in the direct sun, temperatures in the FSPT room ranged from 27.9°C to 45.6°C, and temperatures in the IEPT nursery ranged from 20.3°C to 42.1°C. We did not measure outdoor temperature in the shade. ABTs exceeded 38.0°C in 62 (4%) of the 1393 hourly checks done in the FSPT group (33 infants) and in 20 (1%) of the 1520 hourly checks done in the IEPT group (12 infants;  $p<0.0001$ ; table 3). 42 of these 45 infants returned to normothermia within 1 h; the remaining three (two in the FSPT group and one in the IEPT group) completed treatment for that day without having a follow-up ABT recorded. ABTs below 36.0°C were recorded in 10 (1%) of the hourly checks in the FSPT group (nine infants) and in 24 (2%) of the hourly checks in the IEPT group (14 infants;  $p=0.0467$ ; table 2). 20 of these 23 infants returned to normothermia within 1 h; the remaining three (all in the IEPT group) completed phototherapy that day without having a follow-up ABT recorded. ABTs higher than

38.5°C were recorded in 14 (1%) of hourly checks in the FSPT group (nine infants) and in four (<1%) of the hourly checks in the IEPT group (three infants;  $p=0.0206$ ; table 3). The number of ABTs lower than 35.5°C did not differ significantly between groups (Fisher's exact  $p=0.3544$ ; table 3), and all infants returned to normothermia after appropriate interventions. No infants in either treatment group had a temperature exceeding 38.5°C after an additional back door for ventilation was installed and the floor was painted white in the FSPT room, both of which were completed near the end of November, 2016. No infant in either treatment group showed signs of sunburn or dehydration (table 3).

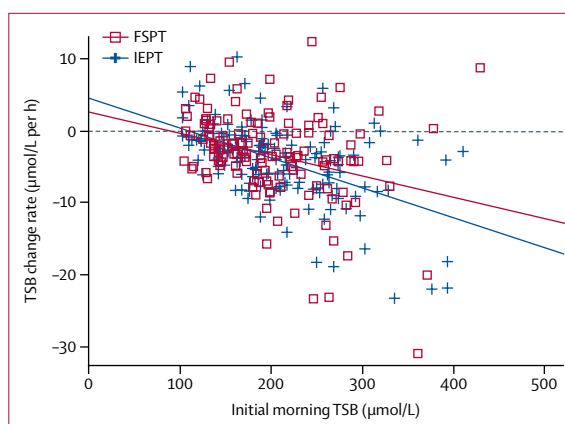
Total serum bilirubin concentrations fell faster when initial concentrations were high than when they were low (figure 3). The mean rate of change in total serum bilirubin concentrations was  $-7.0 \mu\text{mol/L/h}$  when initial concentrations were greater than  $257 \mu\text{mol/L}$  and  $-2.7 \mu\text{mol/L/h}$  when initial concentrations were less than  $257 \mu\text{mol/L}$  ( $p<0.0001$ ). The rate of decrease was significant in both the FSPT ( $p=0.0003$ ) and IEPT ( $p<0.0001$ ) groups, but the difference between the two groups was not significant ( $p_{\text{interaction}}=0.2119$ ).

Two neonates (one in each group) received exchange transfusions after enrolment. Receiving an exchange transfusion was not considered a marker of success or failure. No infant in either group developed acute bilirubin encephalopathy.

## Discussion

In this randomised controlled trial, we showed that the efficacy of FSPT was not inferior to IEPT in the treatment of moderate-to-severe neonatal hyperbilirubinaemia. Importantly, the results from all three analysis modes (intention to treat, as treated, and per protocol) and a post-hoc bootstrap resampling analysis were nearly identical.

We also showed that the rate of decrease in total serum bilirubin concentrations did not differ significantly between the FSPT and IEPT groups, despite the higher irradiance levels delivered by IEPT. A possible explanation is the wider spectral range of FSPT (400–900 nm) compared with IEPT (420–530 nm), which results in the delivery of more irradiance in the green portion of the spectrum, promoting the phototransformation of bilirubin to its more easily excreted product, lumirubin.<sup>25</sup> Salih<sup>26</sup> showed that sunlight is as efficient as artificial light phototherapy when intensities are equivalent, and better than artificial light phototherapy at low intensities. Furthermore, the light footprint of FSPT is uniform whereas that of IEPT declines at the edges,<sup>27</sup> which means that neonates could receive less total body irradiance. In his review<sup>28</sup> of a study by Donneborg and colleagues,<sup>29</sup> Hansen stated that “the site of action of phototherapy is most likely in the capillaries of the skin”. We speculate that there could be more capillary dilatation in skin exposed to FSPT than in that exposed to IEPT because the



**Figure 3: Rate of change in TSB as a function of initial morning TSB for all assessable treatment days**

The dotted line shows zero change. The red and blue lines are linear regression fits for the FSPT and IEPT groups, respectively. TSB=total serum bilirubin. FSPT=filtered sunlight phototherapy. IEPT=intensive electric phototherapy.

skin is slightly warmer in FSPT, thereby increasing bilirubin elimination and allowing for similar efficacy at a lower irradiance level. FSPT also facilitates the use of kangaroo mother care, which is associated with rapid rates of decline in total serum bilirubin concentrations<sup>30</sup>—possibly as a result of improved breastfeeding, increased temperature stability, and generally improved neonatal wellbeing.<sup>31</sup> Our results suggest that FSPT might be more effective in infants with severe hyperbilirubinaemia (ie,  $\geq 257 \mu\text{mol/L}$ ): similar to in other studies, we noted a faster decline in total serum bilirubin concentrations in neonates with high bilirubin concentrations than in those with lower concentrations.<sup>32</sup>

The total serum bilirubin concentration chosen as an inclusion criterion for enrolment was that defined by the American Academy of Pediatrics guideline<sup>20</sup> for high-risk neonates of 35 weeks or greater gestational age. This concentration was chosen because Bowen University Teaching Hospital and many other hospitals in Nigeria generally begin phototherapy at lower concentrations<sup>33</sup> or at approximately 50% of the total serum bilirubin concentration at which an age-specific exchange transfusion would be considered. Generally, physicians in Nigeria use  $342 \mu\text{mol/L}$  as the cutoff for exchange transfusions in term neonates aged 72 h or older.<sup>33</sup> Exchange transfusions are sometimes done at lower total serum bilirubin concentrations than recommended by the American Academy of Pediatrics because phototherapy is of low quality or unavailable, and the high incidence of both haemolysis associated with glucose-6-phosphate dehydrogenase deficiency and acute bilirubin encephalopathy or kernicterus in regions known to have a high incidence of glucose-6-phosphate dehydrogenase deficiency such as Nigeria.<sup>33</sup>

Construction of a stable and durable FSPT aluminium-frame room was an improvement from the canopies that we had previously used. The doors and windows could

be opened or closed and solar-powered fans and exhausts can be turned off or on to minimise risk of hyperthermia or hypothermia, allowing FSPT to be used across a wide range of environmental temperatures and weather conditions. In cold climates, a source of heat can be added and temperatures monitored before placing infants in the room—a safety procedure needed in any new environment.

Limitations of FSPT are that irradiance is dependent upon time of day and cloud cover. Duration of sunlight is finite and treatment can be intermittent if more than one day's treatment is required. Although irradiance is highest (up to 116  $\mu\text{W}/\text{cm}^2/\text{nm}$ ) during sunny days with minimal cloud cover, therapeutic irradiance ( $>20 \mu\text{W}/\text{cm}^2/\text{nm}$ ) can still be delivered on most cloudy days. As in Cremer's landmark study,<sup>9</sup> we recorded decreases in total bilirubin concentrations after only 4 h of sunlight phototherapy. Additionally, in a 1975 article,<sup>11</sup> Dobbs and Cremer noted that intermittent phototherapy produced better results than continuous exposure. Other studies<sup>30,34</sup> have also suggested that, in the absence of severe haemolysis, intermittent phototherapy is at least equivalent to continuous phototherapy. In fact, a study<sup>34</sup> by Sachdeva and colleagues suggested that, in near-term and term infants with moderate hyperbilirubinaemia but without haemolysis, 12 h of phototherapy followed by a 12 h break is as effective as continuous phototherapy for 24 h.

Maintenance of normothermia in neonates undergoing phototherapy is a challenge. Problems with both hyperthermia and hypothermia were noted in both groups in our study. For neonates undergoing FSPT, moist white towels were used successfully for prophylaxis and treatment of hyperthermia as described previously.<sup>17</sup> Importantly, no cases of hyperthermia occurred in the FSPT group after the FSPT room was modified to increase cross-ventilation by adding a second door and a solar-powered exhaust fan, and to reduce heat absorption by painting the floor white. Hypothermia occurred slightly more frequently in the IEPT group than in the FSPT group. Hypothermia as a result of either FSPT or IEPT can be managed with kangaroo mother care.

Ideally, effective IEPT should be available to treat moderate-to-severe hyperbilirubinaemia. However, many studies have shown that devices used in low-income and middle-income countries often provide suboptimal irradiance below the level required even for standard, less intensive phototherapy.<sup>6,35</sup> Thus FSPT is potentially a better treatment than the electric phototherapy that is often routinely available. Although neonates with dangerously high total serum bilirubin concentrations should be referred as soon as possible to facilities with effective IEPT, transfer is sometimes delayed or not possible. FSPT can be used to provide interim treatment while awaiting permission from the family for transfer and while transport, finances, and other supports are being arranged. FSPT can also be used for infants whose

families, because of costs or for other reasons, refuse recommended referral. Compared with no treatment, FSPT will decrease the risk of acute bilirubin encephalopathy and kernicterus.

The safety of phototherapy has been questioned because of DNA damage associated with oxidative stress.<sup>28</sup> However, Uchida and colleagues<sup>36</sup> suggested that the combination of blue plus green phototherapy attenuated oxidative stress and was as effective as blue phototherapy alone, which lends support to the use of broad-spectrum light, such as in FSPT. Furthermore, some data suggest that the duration of phototherapy is more important than the intensity with respect to causing DNA damage.<sup>37</sup> Thus, short sessions of intensive phototherapy might be safer than long, continuous, less-intensive sessions. Despite these concerns, as pointed out by Hansen and others,<sup>16,28,38,39</sup> infants with very high total serum bilirubin concentrations or any kind of symptoms suggestive of bilirubin toxicity, especially those in low-income and middle-income countries with a high incidence of acute bilirubin encephalopathy or kernicterus spectrum disorders, should receive phototherapy with irradiances of at least 30  $\mu\text{W}/\text{cm}^2/\text{nm}$ .

An unavoidable limitation of this study was that clinicians, researchers, and mothers could not be blinded to treatment allocation. Another potential problem could be the unsafe use of unfiltered sun in both high-income countries and low-income and middle-income countries, or the use of FSPT in countries where power is constant and high-quality phototherapy is available. The challenges of managing and monitoring FSPT need to be addressed, including close monitoring of neonatal ABTs and modifications of the treatment environment accordingly, if FSPT is to be scaled up safely. The potential benefits of scale-up are many, and the challenges can be overcome as clinicians work to make severe neonatal hyperbilirubinaemia with acute bilirubin encephalopathy and subsequent death or kernicterus increasingly rare.

Future studies are needed to establish when FSPT alone is adequate to treat moderate-to-severe neonatal hyperbilirubinaemia and when FSPT should be combined with battery-powered IEPT units to provide adequate treatment for infants with moderate-to-severe neonatal hyperbilirubinaemia in areas with inadequate electrical power or phototherapy equipment. Use of FSPT whenever possible could substantially extend the life of batteries and expensive IEPT units, which can be reserved for urgent use.

Supporting the observations made 60 years ago by Ward and Cremer, we have shown that FSPT is no less efficacious than IEPT in reducing total bilirubin concentrations in neonates with moderate-to-severe hyperbilirubinaemia. In the past, concerns about the potentially damaging effects of direct sunlight have prevented the clinical use of FSPT.<sup>40</sup> However, we have shown that, if appropriate technical precautions are



taken, FSPT is a safe, practical, and affordable solution for treating near-term and term neonates in low-income and middle-income clinical settings where sunlight is readily available and electric power or standard phototherapy equipment are unavailable or unreliable.

#### Contributors

TMS conceived and designed the study, approved the design and implementation, coordinated and supervised data collection, and drafted the initial Article. HJV contributed to study design, was responsible for selection of the films and design, procurement, and building of the FSPT treatment room, and provided the design for the electric-powered phototherapy devices. AMB was the study statistician and created and managed the database. YEV contributed to study design and data analyses. OTA coordinated and supervised data collection. IPO supervised data collection. RJW contributed to study design and participated in the film-selection studies. DKS contributed to study design and provided consultation throughout the project. GE set up and supervised the collection of laboratory data. TCL contributed to study design. DAG was the site principal investigator, approved the design and implementation of the study, and coordinated and supervised data collection. TMS drafted the initial Article with input from YEV. All authors critically reviewed and revised the draft.

#### Declaration of interests

We declare no competing interests.

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