Filtered Sunlight for Treatment of Neonatal Hyperbilirubinemia

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SUMMARY

In this randomized, controlled non-inferiority trial, filtered sunlight was compared with conventional phototherapy for the treatment of hyperbilirubinemia in term and late-preterm neonates. The primary end point was efficacy, which was defined as a rate of increase in total serum bilirubin of less than 0.2 mg/dL/h for infants up to 72 hours of age or a decrease in total serum bilirubin for infants older than 72 hours of age who received at least 5 hours of phototherapy. Authors pre-specified a non-inferiority margin of 10% for the difference in efficacy rates between groups. The need for an exchange transfusion was a secondary end point. Safety, which was defined as the absence of the need to withdraw therapy because of hyperthermia, hypothermia, dehydration, or sunburn, was also assessed. Of the total 447 infants, 224 were randomly assigned to filtered sunlight and 223 to conventional phototherapy. Filtered sunlight was efficacious on 93% of treatment days that could be evaluated, as compared with 90% for conventional phototherapy, and had a higher mean level of irradiance (40 *vs.* 17 $\mu W/cm^2/nm$; $P<0.001$). No infant met the criteria for withdrawal from the study for reasons of safety or required an exchange transfusion. Authors concluded that filtered sunlight was non-inferior to conventional phototherapy for the treatment of neonatal hyperbilirubinemia.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Phototherapy using blue light is recognized as a standard of care for the management of majority of neonates with jaundice, and hence is widely practiced around the globe. In addition to the wavelength of light used, other issues for effective phototherapy include mean (and not only peak) irradiance, rate of irradiance decay, and adequacy of exposure of infants' body surface [1,2].

This publication [3] reports a non-inferiority randomized controlled trial (RCT) comparing filtered sunlight (Intervention) *versus* conventional photo-therapy (Comparison) in infants with mild to moderate neonatal hyperbilirubinemia (Population) in terms of efficacy and safety (Outcomes). The authors justified this trial on the basis of individual and societal consequences of inadequately treated neonatal hyperbilirubinemia, practical difficulties with delivering appropriate phototherapy in resource-limited settings, and their previous research experiments with filtered sunlight. The potential limitations with using conventional phototherapy include (non) availability of appropriate units, cost of individual units, requirement of uninterrupted electricity supply, and need to measure irradiance periodically to ensure efficacious delivery. These can be challenging in many resource-limited settings.

Prior to the RCT, the investigators demonstrated the capability of various glass-tinting film materials to selectively transmit light with wavelength 400 to 520 nm (blue light) while restricting ultraviolet A and infrared wavelengths [4]. They then published a protocol [5] for comparing filtered sunlight *versus* conventional photo-therapy in near-term neonates <2-week-old in a hospital setting in Lagos (Nigeria), using a non-inferiority RCT design. Results from an observational study [6] suggested that filtered sunlight was safe and efficacious in such infants, although about one-third of infants required brief periods of omission on account of hyper- or hypothermia. Simultaneously, they also published data from a survey of mothers of infants treated with filtered sunlight and reported high levels of maternal satisfaction with this modality [7]. In a sense, the preliminary work is important for understanding and appraising this RCT [3].

Critical appraisal: ***Table*** **I** highlights the methodological characteristics of the trial using the standard Cochrane Risk of Bias tool [8]. Overall, the trial can be considered to have a high risk of bias. This is mostly because of unclear allocation sequence generation and absence of blinding. The latter could have been relatively easy for the efficacy component by ensuring that personnel measuring serum bilirubin were blinded to the allocation assignment. Of course, it would be more complicated to blind the outcome assessors for the safety component. It should also be

TABLE I. METHODOLOGICAL APPRAISAL OF THE TRIAL

Domain	*Description*	*Judgement*
Sequence generation	Block randomization method with variable block sizes (2-10) was used. However the specific method used to generate the sequence was not described.	Unclear
Allocation concealment	Allocation was made using serially numbered slips placed in opaque sealed envelopes. These were prepared off-site and opened in sequence after randomization.	Adequate
Blinding	There was no blinding for any of the measured outcomes *viz* efficacy (measured by trends in serum bilirubin and/or need for exchange transfusion) or safety (development of hyper- or hypothermia, dehydration or sunburn).	Inadequate
Incomplete outcome data	A total of 447 infants were randomized; 224 in the intervention arm and 223 in the comparison arm. 14 participants did not receive the planned treatment; 11 in the intervention arm and 3 in the comparison arm. Thereafter 18 and 13 infants respectively could not be evaluated for efficacy suggesting a total attrition (from randomization) of 13% in the intervention arm and 7% in the comparison arm, although these are not the numbers shown in the flow chart. Although reasons for attrition are clearly described and appear uncontrollable, the total number of days of treatment (available for analysis) exactly matched with the number planned *a priori*. This appears to be a remarkable coincidence. The number of randomized infants included in the safety analysis is unclear. Data analysis is reported to be intention-to-treat.	Unclear
Selective outcome reporting	All outcomes planned a priori have been reported	Adequate
Other sources of bias	No obvious sources of bias are evident.	Adequate
Overall assessment		High risk of bias

mentioned that the previous experiments by the investigators [4,6,7] pointed towards a potentially beneficial effect of filtered sunlight. This could be expected to bias the investigators towards the intervention; therefore blinded outcome assessments are even more important.

The investigators incorporated some methodological refinements in their study. First, this RCT was designed as a non-inferiority trial despite availability of *in-vitro* evidence suggesting superiority of sunlight [9]. The investigators' own observational study showed very high efficacy (92%) with filtered sunlight. These observations could have prompted them to opt for a superiority trial (*i.e* proving that filtered sunlight is superior to conventional phototherapy). In such a study design, a non-significant difference in efficacy does not automatically mean that the two arms have equivalent efficacy. Therefore, in such a setting where an effective treatment (phototherapy) is the standard of care, a non-inferiority trial (where the design is to show that the intervention is not much worse than the comparison), is appropriate. To achieve this, it is required to demonstrate that the 95% CI of the treatment effects in the two arms lie within a pre-specified narrow range (10% for efficacy and 5% for safety in this trial). This generally necessitates a larger sample size than conventional superiority trials. In fact, the investigators planned to recruit 924 infants based on these considerations, but chose to work with the 'number of treatment days' rather than 'number of infants', thereby reducing the sample size requirement to less than half.

Unfortunately the reduced sample size made it feasible to complete the trial within 10 months (November 2012 to September 2013) making it impossible to study the efficacy during two months of the year. In general, the average highest and lowest temperature in Lagos during the missing months (September and October) are not very different from the other months [10]; however these are two of the wettest months, with precipitation during at least one-third of the days. Naturally, a twelve month period of observation would have given a better understanding of the effect of ambient climatic conditions.

Despite high overall efficacy (over 90% as per the investigators' definition), the rate of bilirubin decline in the conventional phototherapy arm appears to be somewhat lower than in other trials of phototherapy [11-13]. Of course, it may not be appropriate to compare efficacy across trials unless there is homogeneity in terms of population, intervention and timing of outcome measurement. The importance of this is that a less-than-adequate rate of bilirubin decline in the phototherapy arm

would create a spurious impression of greater efficacy in the filtered sunlight arm, as the authors have reported [3]. This 'spurious' superiority is itself doubtful because there was overlap between the 95% confidence intervals, suggesting comparable effects.

Although the investigators reported comparable safety in the two arms of the trial [3] for most outcomes measured, there was greater incidence of hyper- and hypothermic episodes in infants receiving filtered sunlight. The comparability was achieved through stringent hourly monitoring of body temperature, and immediate institution of counter measures. This suggests that routine clinical use of filtered sunlight would necessitate stringent monitoring for adverse effects and facilities to correct these. This may entail greater manpower and/or resource usage, negating the putative benefits of availability at the point-of-care and lower cost (of the equipment) with filtered sunlight.

The comparable absence of withdrawals (from both groups) on account of need for exchange transfusion attests to the inclusion of relatively milder cases and lower thresholds for treatment. It is unclear whether the intervention would perform similarly in real-world conditions.

A finding that was not sufficiently emphasized is that one-seventh of infants receiving filtered sunlight required phototherapy after daylight hours [3]. This occurred despite initiating treatment at a lower threshold serum bilirubin than the standard guideline of the American Academy of Pediatrics [3,14]. This has two important implications. First, it is likely that treating at the usual thresholds would necessitate continuing the intervention in a larger proportion of infants. Second, the observation mandates backup phototherapy units thereby limiting its usage to health-care facilities with adequate manpower and resources to manage sick neonates. This practically neutralizes the proposed advantages of filtered sunlight described above. A minor but potentially important point is the stringency with which irradiance was measured in this trial. The intention was to measure irradiance once daily in the phototherapy arm and hourly in the filtered sunlight arm. If this was followed, we would expect 325 readings in the phototherapy arm, whereas only 293 are reported. We would also expect 1876 readings in the filtered sunlight arm (maximum of 7 readings per day × 268 days) whereas 2959 are reported. These deviations from the protocol have not been explained.

How would mothers respond to offering their babies filtered sunlight as opposed to conventional phototherapy? On the one hand, sunlight exposure was a widely practiced traditional remedy for newborn jaundice; on the other hand, this has been actively discouraged on account of potential harmful effects of ultraviolet and infra-red radiation. The authors' previous study [7] suggested a high level of maternal satisfaction with filtered sunlight, using a five point Likert scale. However in the survey, mothers reported a median score of at least 4 for all issues on which feedback was sought (filtered sunlight was only one of these) suggesting high level of satisfaction with the overall health-care delivery system in general, rather than filtered sunlight in particular.

Extendibility: It is clear that usage of filtered sunlight for neonatal jaundice can be considered only in infants with relatively mild jaundice and with intensive monitoring, as well as the presence of backup phototherapy units. This severely restricts the potential of using it as a primary health-care delivery measure in rural areas and at the point-of-care.

Some of the considerations that could make it easy to extrapolate the findings of this trial [3] include abundance of ambient sunshine in most parts of India, during most of the year; and the potential for constructing filtered sunlight tents at low cost. The issues that could preclude direct extrapolation include the geographic (latitude) location of Lagos and the relatively uniform high skin phototype score of participants in the trial. It is also unclear how the irradiance would vary with environmental air pollution and smog/fog in urban settings in Northern India.

Conclusions: This RCT suggests that filtered sunlight could be non-inferior to conventional phototherapy for mild to moderate neonatal jaundice in terms of efficacy and safety, in the presence of adequate facilities for backup phototherapy and intensive monitoring. These effects were evident at an irradiance level more than twice that of conventional phototherapy. There are several methodological and feasibility considerations that preclude the immediate application of filtered sunlight as a viable alternative to conventional phototherapy.

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Neonatologist's Viewpoint

Neonatal hyperbilirubinemia is a common problem in the first few days of life. Phototherapy is the standard treatment for the management of neonatal hyperbilirubinemia, and most cases can be successfully controlled by its use. In few cases where phototherapy fails, exchange transfusion can be employed to rapidly lower serum bilirubin levels to safe limits. Although phototherapy units are available in resource-limited settings at affordable costs, the performance of these units leaves much to be desired due to low irradiance (energy output) or erratic electric supply. Due to this, many newborns are exposed to sub-therapeutic irradiance levels.

In this randomized controlled trial (RCT), Slusher, *et al.* [1] compared filtered sunlight with conventional phototherapy for the treatment of neonatal hyperbilirubinemia in term and late-preterm newborns in a Nigerian hospital. Authors found filtered sunlight as effective as conventional phototherapy for the treatment of neonatal hyperbilirubinemia. Both forms of phototherapy were comparable in safety; although temperatures higher than 38 ^{o}C occurred in 5% of newborns receiving filtered sunlight, and in 1% of those receiving conventional phototherapy (P<0.001). However, no newborn was withdrawn from the study for reasons of safety. Interestingly, authors found much higher level of irradiance with filtered sunlight (40 *vs*. 17 μW/cm^2/nm, P<0.001).

Exposing jaundiced newborns to sunlight is practiced in many societies, although health professionals do not advocate its use due to doubtful efficacy and safety concerns regarding sunburn, hyperthermia or exposure to ultraviolet radiation [2]. There are also issues of availability of sunlight round the clock and during cloudy weather, and its use during winter months when the risk of hypothermia is high. The present study has refuted some of these concerns and demonstrated that filtered sunlight is equally effective and safe. The authors used special film canopies which filtered out most ultraviolet and some infrared (heat) radiation while allowing passage of blue light. Unlike conventional phototherapy, where a newborn requires separation from mother to receive phototherapy, filtered sunlight has the advantage of maintaining mother-infant interaction with all its attendant benefits, if a large enough canopy is used to accommodate the mother-newborn dyad. This is a low cost technology and has other advantages as well, such as availability in remote regions, use of energy source which is essentially free, and also eco-friendly. By virtue of its nature, filtered sunlight cannot be used to treat hyperbilirubinemia in sick newborns who require close monitoring in a NICU environment.

Before filtered sunlight can be adopted on a wider scale to treat neonatal hyperbilirubinemia, studies are needed to assess its impact in other settings. A limitation of this study is that it included newborns with serum bilirubin levels below 15 mg/dL. Whether filtered sunlight will be equally effective at higher bilirubin values or rapidly rising bilirubin levels needs to be studied further. At high bilirubin levels, nighttime phototherapy will be required. This occurred in 13% of newborns in present trial. Thus conventional phototherapy is not going to disappear. The filtered sunlight will complement conventional

phototherapy rather than replace it. The present trial has vindicated the long-held community practice of exposing jaundiced newborns to sunlight, albeit in a modified manner.

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Public Health Viewpoint

This article comes at an appropriate time as India gears up to reduce neonatal mortality rate to single digit numbers by 2030 through the recently launched India Newborn Action Plan – the Indian version of the Every Newborn Action Plan – at a global level. However, there is a huge distance to be covered between research, policy and practice.

Before moving on to the policy and practice part, the non-inferiority of this interventions will have to be proved in Indian conditions as factors such as the differences in skin colors of children, and variations in temperatures and sunlight during different times of the year can affect the study's outcomes. There are hardly any community-based data on the burden of neonatal hyperbilirubinemia from India. This leads to difficulty in priority setting of this issue in the national public health context. Currently the Indian public health system attempts to deal with neonatal hyperbilirubinemia by phototherapy units at Sick Newborn Care Units at secondary and higher centers under the RMNCH+A strategy. The researchers have proved that filtered sun light is not inferior to phototherapy units in reducing the serum bilirubin levels in neonates. This gives a major boost to make community-based interventions for a health problem which has so far been thought to be managed only at the institutional level.

However, it will require trained health workers to carry on this initiative successfully. Public health is about behavior change. Ensuring an effective community participation using Behavior change and communication strategies will be required to make this approach effective. Another concern is of open space availability to carry out this intervention. In urban slums, in contrast to the rural areas, availability of open spaces is a major constraint, due to overcrowded areas.

Community-based efficacy and feasibility studies in India are required to take this research further to benefit thousands of children suffering from neonatal hyperbilirubinemia.

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