Uniform national guidelines do not prevent wide variations in the clinical application of phototherapy for neonatal jaundice

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Short title: Phototherapy guidelines don't prevent variations

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Abbreviations: TcB, transcutaneous bilirubinometry; TSB, total serum bilirubin; NICU, neonatal intensive care unit; GA, gestational age; ELBW, extremely low birth weight.

FINANCE

This study was funded by Renée and Bredo Grimsgaard's Foundation.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ABSTRACT

Aim: This study compared the use of phototherapy for neonatal jaundice in all 21 Norwegian neonatal intensive care units (NICUs) from 2013-2014 in order to improve practice.

Methods: Information on all types of phototherapy devices were collected and irradiance was measured from random units at 20cm and 50cm from the light source. We gathered information on local practice rules, including the use of single, double or triple phototherapy, how infants were positioned, the frequency of blood sampling, rules for using reflective surfaces and interrupting phototherapy. In every NICU we asked one nurse with more than five years of experience, and one with less than one year, to set up phototherapy equipment, then measured the irradiance and distance.

Results: Photodiodes were the most common of the eight types of phototherapy devices used. Rules for the distance from the device to the infant varied from 10-40cm and in practice they varied from 15-48cm, with irradiance ranging from 11.1-56.1 W/m². There were significant variations between NICUs with regard to the overall treatment duration and duration in most birth weight categories.

Conclusion: There were considerable variations in phototherapy practices among Norwegian NICUs. In particular, the significant variations in duration need to be addressed.

Key words: Clinical guidelines, Hyperbilirubinaemia; Neonatal jaundice; Phototherapy; Quality assurance.

Key notes

- This study compared the use of phototherapy for neonatal jaundice in all 21 Norwegian neonatal intensive care units (NICUs) from 2013-2014 in order to improve practice.
- Information on all types of phototherapy devices were collected and the local practice rules were compared with what actually happened in practice,
- There were considerable variations in phototherapy practices among Norwegian NICUs and, in particular, the significant variations in duration need to be addressed.

INTRODUCTION

Phototherapy for neonatal jaundice is probably one of the most common treatments newborn infants receive in the neonatal intensive care unit (NICU), but there appear to be significant variations in its practical application (1,2). Guidelines vary both between and within countries (3). Although these guidelines contain recommendations for effective irradiance and suggest total serum bilirubin thresholds for starting phototherapy treatment (3-5), bilirubin experts agree that the scientific basis for many of the suggestions do not meet present-day expectations for evidence-based medicine.

Norway has had national consensus guidelines for neonatal jaundice and phototherapy since 2006 (3). From 2006-2015 we only had one documented case of kernicterus (6), which is an incidence of about one in 600,000 births, and this occurred because the rules in the guidelines for follow ups were not followed. In our other paper in this issue of *Acta Paediatrica* (7), we show that the average duration of phototherapy in Norwegian NICUs was shorter than in most other published studies of phototherapy. Thus, we could argue that our Norwegian guidelines for phototherapy work well.

However, because discussions within the neonatal community suggested that there might be variations in practice patterns, despite the existence of national guidelines, we decided to investigate both the epidemiology of phototherapy (7) and the local rules and conditions that might have an impact on the use and efficacy of phototherapy. Such local rules and conditions could include the types of phototherapy devices, frequency of blood tests for total serum bilirubin (TSB), the use of single, double or triple phototherapy and other efforts to increase spectral power, positioning and rules for feeding,. To the best of our knowledge this was the first nationwide, prospective study on managing neonatal jaundice.

MATERIALS AND METHODS

Population

The study was performed in all 21 Norwegian NICUs – seven level three and 14 level two - during a one-year period from 1 September 2013 to 31 August 2014. During the study period, 5,382 infants were admitted to the NICUs, representing 9.0% of the total population of newborn infants in Norway (7).

Phototherapy duration

Phototherapy was recorded electronically every day in the Norwegian Neonatal Network database. Briefly, the daily entry page of the database contains a box which, when ticked, requires the number of phototherapy hours to be entered before it can move on to the next day. The software can also record the start and end times for phototherapy and this provides further confirmation of the number of hours recorded on the daily recording page. A project collaborator was responsible for the quality control of the registration procedures in every NICU. Further details on the recording procedures are described in our other paper in this issue of *Acta Paediatrica* (7).

Irradiance measurements

During the site visits the first step was to measure the irradiance in Watt/m^2 , as detailed later, from a random sample of three phototherapy units at a vertical distance of 20cm and 50cm from the light source. Then, two nurses - one with more than five years of neonatology experience and one with less than one year of experience - were asked to set up the equipment, as dictated by the clinical routines in their department. Both were unaware that the other nurse had been given the same task. We then used a manikin that was the size of a term newborn infant and lying supine, which had been brought along for this purpose, to measure irradiances at the level of the abdominal surface and of both flanks, as well as the distance from the manikin to the light source. The irradiances levels were measured with an LMT Pocket-Lux 2 photometer (LMT Lichtmesstechnik GmbH, Berlin, Germany), which has

a sensitivity spectrum of 388-555 nm, peaking at 475 nm. Irradiance measurements are presented in W/m^2 because our photometer gives the results in this unit.

We wanted to assess the relationship between the W/m^2 values returned by the LMT irradiance meter used in the present study with $\mu\text{W/cm}^2/\text{nm}$, which is often used as reference values for phototherapy irradiance (4). To do this, we concurrently measured irradiance from a neoBLUE phototherapy device with the LMT irradiance radiometer referred to above, as well as with the neoBLUE irradiance radiometer (Natus Medical Inc., California, USA) at distances of 10, 20, 30, 40 and 50cm. Across these distances the neoBLUE irradiance radiometer consistently returned numerical values for irradiance in $\mu\text{W/cm}^2/\text{nm}$ that were 25% higher than the numerical values returned by the LMT irradiance meter in W/m^2 . Furthermore, in previous studies (8), sample setups had been measured with an Air Shields PR III Phototherapy Radiometer (Air Shields, Pennsylvania, USA), which yielded values in $\mu\text{W/cm}^2/\text{nm}$ and were found to be within 10-15% of the numerical measures provided by the Pocket-LUX meter.

Variables associated with local routines and procedures

Data and variables pertinent to local neonatal jaundice treatment procedures were obtained by site visits to all these NICUs. These variables included: 1) the types of phototherapy units available; 2) local rules for the distance between the phototherapy devices and infants; 3) the use of single, double or triple lights and the indications for such use; 4) the use of reflective material, for example white linen, in phototherapy set-ups; 5) local routines for changing the positions of infants during phototherapy; 6) methods for bilirubin screening; 7) local guidelines for TSB sampling during phototherapy, such as frequency and interval; 8) local practices regarding fluid management during phototherapy; 9) the use of infant formulas or other adjuvant treatment and 10) whether interrupting phototherapy for breastfeeding was permitted.

Ethics

The South-Eastern Regional Committee for Medical Research Ethics reviewed the study and classified it as a quality control study that did not need consent from individuals in the database or their proxies (2013/287). Accordingly, the study was then reviewed and approved by patient safety representatives at Oslo University Hospital (2013/17162).

Data handling and statistics

Data were summarised using descriptive statistics. The duration of phototherapy among hospitals within different birth weight categories was compared by ANOVA. Since the distribution of birth weight categories varied significantly across NICUs, Z-scores for phototherapy duration were calculated within each birth weight category to compare the overall mean phototherapy duration among NICUs. Due to the skewed distribution of both the phototherapy and Z-scores, log-transformed values were used when estimating p values. We had measured irradiance at distances of 20cm and 50cm and these values were compared using ANOVA. Data from test set-ups by the nurses were compared with the t-test. Significance was defined as $p < 0.05$.

RESULTS

Phototherapy duration

There were significant differences in phototherapy duration among NICUs in all birth weight categories of at least 1,500g, as well as for the total treated population (Table 1). For example, the phototherapy duration in the group with a birth weight of greater than 2,500g ranged from 15.6 to 42.7 hours.

Irradiance measurements

The mean, standard deviation (SD) and 95% confidence interval of the irradiance measured from up to three sample phototherapy devices, if available, was 25.7 ± 6.6 (22.7-28.8) W/m² at 20cm and 11.3 ± 5.2 (8.8-13.7) W/m² at 50cm. The ranges of the individual

measurements were 16.0 - 64.4 W/m² at 20cm and 4.6 - 36.7 W/m² at 50cm (Figure 1). There was a highly significant difference in mean irradiance among the NICUs, both at 20cm ($p=0.0106$) and 50cm ($p<0.001$). It should be noted that in NICU number 11, where extremely high irradiance values were measured, the phototherapy units were checked by technical maintenance staff following the site visit. The units were found to be mal-adjusted, which accounted for the higher than intended output. In one NICU they only used phototherapy blankets, which could not be measured according to our study design. None of the NICUs routinely measured the irradiance during ordinary phototherapy. In fact, only one NICU had a radiometer on site that could be used, if needed, and the others relied on scheduled maintenance by engineering staff.

Values for the means and SDs were not significantly different between the less and more experienced nurses as far as the distance from the lights to infant (28.1 ± 7.3 versus 27.1 ± 7.7 cm). Nor were there differences in the irradiance achieved in the test set-ups (26.0 ± 6.9 versus 27.0 ± 10.9 W/m²). However, the data provided a wide scatter, with the range of distance from 15-48cm, and the irradiance from 11.1-56.1W/m² measured at the abdominal surface in the supine position.

Phototherapy devices in use

There were eight different types of phototherapy devices used in Norwegian NICUs (Table 2). It was apparent that light emitting diode lamps were the predominant light source, either overhead or from below. Some NICUs used more than one type of device. All NICUs, except one, had a schedule for maintaining their phototherapy units: 19 NICUs carried these out every year and one did so every five years.

Practical aspects of phototherapy set up and use

Local written rules for setting up the phototherapy device existed in 18 of the 21 NICUs and these specified considerable variation with regards to the recommended distance between the light source and the infant (Table 3). There were no recommendations in the

other three units. Fiberoptic pads were only used in one unit, one NICU used a fixed distance due to the device construction and in the third the distance was not mentioned in their local procedure.

Data that show the variations between NICUs for some common phototherapy practice routines are shown in Table 4. There were eight NICUs that routinely used transcutaneous bilirubinometry (TcB) for initial bilirubin screening and then followed that up with TSB, either by diazo or CO-oximetry / multiple wavelength analysis methods if the TcB results were high (Table 5). The remaining 13 NICUs screened for jaundice by analysing TSB directly, using either diazo or CO-oximetry or a combination of both methods. This involved initial screening with CO-oximetry and diazo analysis as a supplementary method if the CO-oximetry result was above the intervention limits. In 17 of the 21 NICUs, TSB was checked from less than once a day to a maximum of twice daily during on-going phototherapy, while in three NICUs the TSB could be checked up to three to four times a day. Only one NICU appeared to have no fixed rule. Analyses of the relationships between some practice routines and phototherapy duration are presented in Table 6.

The decision to initiate or stop phototherapy was normally delegated to the baby's nurse, who plotted the TSB value on the phototherapy chart and decided whether the mark was above or below the intervention line on the graph. The nurse always communicated this decision to the baby's physician, and, if they were in any doubt, they would discuss the case with the attending physician before implementing any change in therapy.

DISCUSSION

The treatment of neonatal jaundice made two giant leaps forward in the 20th century. The first was the introduction of exchange transfusion (9) and the second was the discovery of the therapeutic effect of phototherapy (10). It has been argued that the main purpose of phototherapy is to avoid the need for exchange transfusions. However, as exchange transfusions have become increasingly rare (11), it could equally be argued that phototherapy

is currently the leading tool to avoid kernicterus. If this argument is accepted, the Norwegian guidelines for managing neonatal jaundice are highly successful, as the incidence of kernicterus, which was one in 600,000 births from 2006-15, was significantly lower than reported from other industrialised countries (12,13).

Despite the existence of national uniform guidelines on the limits of phototherapy, this paper, and our other paper in this issue (7), show that considerable variation occurred in clinical practice. There were significant variations in the duration of phototherapy between the NICUs in all birth weight categories of at least 1,500g. In the two birth weight categories of less than 1,500g, the data showed a considerable spread (Table 1), from 15.0-65.8 hours in infants weighting less than 1,000g at birth and from 21.5-47.5 hours in the 1,000-1,499g birth weight category. As shown, the SDs were quite wide and the number of patients in these birth weight categories was very limited in the majority of NICUs. Only five hospitals reported more than 10 patients with birth weights of less than 1,000g and eight hospitals reported more than 10 patients with birth weights of 1,000-1,500g, with only one hospital reporting more than 20 patients. Thus, the lack of significance is likely to reflect, at least partly, insufficient power in these comparisons.

Our study had a pure observational design. Therefore, the data on rules for the distance between the light and infant, the frequency of TSB sampling and observations and measurements from site visits could not be organised into simple categories for statistical comparisons with the duration of phototherapy. It is, therefore, not surprising that we did not find any statistically significant relationships to the duration of phototherapy in the overall data, rules for the distances between the lights and infants, TSB sampling frequency or irradiance measurements during the site visits (Table 6). This does not rule out the possibility that such relationships exist, as was possibly suggested by the analyses in some birth weight subgroups (Table 6). Thus, both more frequent TSB sampling and higher spectral power, which would be achieved by higher irradiance and shorter infant to light distances, could contribute to shortening the duration of phototherapy. In fact, both logic and the existing

knowledge of the biology of phototherapy strongly suggest that such a relationship may be present.

The Norwegian guidelines that were in place for the treatment of neonatal jaundice at the time of this study, recommended that phototherapy should be administered to the maximum attainable body surface area at a level of at least $20 \mu \text{ W/cm}^2/\text{nm}$ (3). Our data showed that when they were measured in a standardised way at a distance of 20cm, the phototherapy units in almost all of the NICUs we tested achieved a median irradiance at, or above, 20 W/m^2 (Fig. 1). When we added 25% to the numerical values, according to the comparison measurements cited above, this corresponded to approximately $25 \mu \text{ W/cm}^2/\text{nm}$, which was well above the value of $20 \mu \text{ W/cm}^2/\text{nm}$ suggested in the guidelines (3). However, the ranges of irradiance values from both the sample phototherapy units and from the test set-ups by the experienced and less experienced nurses were wide and, in many instances, the irradiance values were well below the target value. This suggests that unless the irradiance was routinely measured every time a baby was put under the phototherapy lights, it was the luck of the draw as to whether that baby received the level of irradiance they needed. Despite the fact that the 2006 national guidelines recommended having a photometer on site (3), only one of the 21 NICUs actually possessed a photometer for irradiance measurements and none had rules that prescribed routinely measuring irradiance. Therefore, obvious suggestions for quality improvements are to invest in an appropriate photometer and to routinely measure irradiance every time phototherapy is initiated. Labelling photometers with the irradiance values laid down by the local rules would also help to facilitate their implementation.

Measuring irradiance at the level of an infant's skin depends on how the output of the phototherapy unit is adjusted and the distance between the light source and the infant (14). Therefore, this distance should be kept as short as compatible with the type of light source. If an infant is being nursed in an incubator, the incubator roof would obviously limit the ability to bring the light source closer.

The 2006 Norwegian guidelines suggested a distance of 10-20cm (3). When we measured the test set-ups carried out by the nurses, the distances ranged from 15-48cm with a mean of approximately 28cm. About half of the nurses did not measure the distance when they set up the phototherapy unit, with no difference between the experienced and less experienced nurses. This suggests that, in everyday practice, the importance of the light to infant distance was not given enough attention. One suggestion for quality improvement could be to attach a 20cm rod to every phototherapy device, so that every time the devices were used the correct distance from the light source to the infant's skin could be easily measured.

Spectral power, which is the irradiance multiplied by the size of the irradiated skin surface, is a key concept in phototherapy (14). It can be increased by increasing both irradiance and the area of skin that receives therapeutic light (15). In accordance with the national Norwegian guidelines (3), all NICUs had local rules that prescribed the use of reflecting cloths to improve the dispersion of overhead phototherapy light. In the test set-ups, approximately 80% of the nurses included these cloths, with no difference between the nurses with more or less experience. The use of double or triple phototherapy can also increase spectral power, but this is a rather cumbersome way to achieve this goal and was not commonly used in the NICUs (Table 4).

In 18 of 21 NICUs the position of the infants during phototherapy was routinely alternated every three to four hours (Table 4). An international survey published in 1996 showed that the position of infants during phototherapy was routinely alternated in two-thirds of the NICUs in Europe (1). This was also common practice in Denmark and Norway (16). However, it has also been shown that routinely alternating the infant's position during phototherapy does not increase the effect of phototherapy, presumably because it happens in the capillary circulation near the skin's surface (16). This was compatible with studies that showed that formation of bilirubin photoisomers was detectable within a few minutes of

turning on phototherapy lights, long before diffusion from the skin tissue could have occurred (8,17).

Screening for neonatal jaundice by TcB was less common than screening by TSB in our study. TcB screening is common in maternity units and it is not clear why it was used less in NICUs. One reason may be that TcB cannot be reliably used in infants receiving phototherapy and another reason may be that most of the infants who received phototherapy in Norwegian NICUs were not primarily admitted because of neonatal jaundice (7). In these infants, neonatal jaundice may have been detected as a by-product of blood gas and electrolyte analyses, which also incorporate TSB by CO-oximetry. Alternatively, TSB, may have been part of a larger panel of tests in a diagnostic work-up. Also, the greater precision of TSB versus TcB is likely to be warranted in sick infants. However, Ebbesen et al showed that TcB may be a useful screening tool, even in NICUs, for infants born at more than 32 weeks of gestation (18). Thus, it is quite possible that more NICUs in Norway may find this tool useful.

Most NICUs checked TSB 0-2 times per day during on-going phototherapy. In the 2004 American Academy of Pediatrics' guidelines, the recommended frequency for follow-up TSB tests during phototherapy were tailored to the severity of neonatal jaundice (4). Another argument for more frequent TSB follow up during phototherapy would be to keep the duration of phototherapy short. In studies that have shown that phototherapy could be toxic, the determining factor was the duration of phototherapy, not irradiance (19). Other reasons for limiting the duration of phototherapy are to increase the parents' interactions with the baby, as well as making nursing access and observations less cumbersome. Therefore, although the mean duration of phototherapy in Norwegian NICUs was shorter than in many other studies (20-22), the significant differences in duration between the NICUs that we observed suggest that an even shorter duration may be possible for many NICUs.

All neonatal units in Norway routinely allowed phototherapy to be interrupted for 30-60 minutes for breastfeeding, clinical examinations, parental visits and skin-to-skin contact

(Table 4). This was in accordance with studies that concluded that intermittent phototherapy was as effective as continuous phototherapy (23,24). Routinely increasing fluid supplementation during phototherapy is not indicated, as specifically stated in the national guidelines, and only one NICU continued to follow this out-dated practice. Providing formula supplements during prolonged or excessive jaundice has been supported by the literature (25), but was practiced by less than half of the NICUs in our study (Table 4).

Evidence suggests that prolonged exposure to phototherapy lights may be detrimental to jaundiced infants and that efforts should be made to keep exposure short, particularly in the most immature infants (26). This can be achieved by avoiding prophylactic phototherapy, not starting phototherapy until intervention levels have been surpassed and stopping phototherapy as soon as the TSB falls below the intervention line by a predetermined number. The Norwegian national guidelines recommend 20 $\mu\text{mol/L}$, but this was a pragmatic choice without a real evidence base. Another practice that could limit the length of exposure to phototherapy lights is the frequency of TSB sampling. It seems obvious that keeping exposure brief is less likely to be achieved if TSB is only sampled once rather than two to four times a day. The evidence base is once again inadequate, but applying a common sense approach to each infant seems wise. The most vulnerable infants appear to be extremely immature infants receiving ventilator support (26). Using a blood gas machine with integrated TSB measurements makes reasonably frequent sampling possible using very small amounts of blood.

Guidelines are valuable as a quality assurance tool. In an effort to keep the 2006 guidelines brief and easily accessible, they did not cover all the aspects of managing neonatal jaundice in detail. The finding that there were some variations between local guidelines was therefore to be expected. An important question seems to be whether such variations can have a negative impact on outcomes, and therefore should result in increased efforts to improve quality, or whether they should be accepted because no impact can be detected on the relevant measures of quality. Considering the range and variability of the values shown in this study,

with regards to both irradiance and the light to infant distance, we are tempted to suggest that few other therapies routinely employed in NICUs are likely to be deployed with such apparently low precision as phototherapy.

Given the fact that phototherapy is commonly used in neonatal medicine, we are concerned that our study, as well as other studies with a more more limited scope (2,22), seemed to show that insufficient attention was being paid to precision and quality. Lack of adherence to the rules for using phototherapy devices resulted in unpredictable spectral power. While this may not be a significant risk for an infant whose TSB values barely transcend the intervention levels, it could mean the difference between future health or a life with the sequelae of kernicterus for an infant with extreme TSB values and evidence of acute bilirubin encephalopathy.

Educating and training staff is crucial. Because kernicterus is so rare, the real threat of neonatal jaundice may be forgotten and only conscientious efforts will keep it in focus. In-service orientation should be scheduled for all new trainees, but nurses and doctors transferring from other NICUs should also be included. Following our findings, and, as an aid to staff education and training, the Norwegian Pediatric Association has revised the guidelines and has also published three supplementary documents that explain the recommended procedures for managing neonatal jaundice in greater detail (27). This has included increasing the goal for irradiance in effective phototherapy to more than $30 \mu \text{w/cm}^2/\text{nm}$

CONCLUSION

We found that, despite the existence of uniform national guidelines, there was a wide variation in phototherapy practice among NICUs in Norway. Although the treatment of neonatal jaundice has a high success rate in Norway, as measured by the duration of phototherapy and the very low incidence of kernicterus, suboptimal phototherapy may sometimes be applied. This may carry particular risks for patients with extreme neonatal

jaundice. Therefore, awareness and knowledge of all the factors that influence the effectiveness of phototherapy, as well as increased attention to the practical details, is very important to improve the quality of phototherapy.

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