Transcutaneous Bilirubinometry in Jaundiced Neonates: A Randomized Controlled Trial

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BACKGROUND: For evaluation of jaundiced neonates, serum bilirubin (SB) or transcutaneous bilirubinometry (TcB) is used. Few data are available on the quantitative reduction of blood sampling by using TcB.

abstract

METHODS: We conducted a randomized controlled trial in hospitalized jaundiced neonates \geq 32 weeks' gestational age. In the intervention group, TcB was used and in the control group the decision to obtain a blood sample for SB was based on visual and clinical assessment. Outcome measure was the number of blood samples before phototherapy. When TcB was <50 µmol/L below the threshold for phototherapy, SB was obtained. The decision to start treatment was always based on an SB value.

RESULTS: A total of 430 were randomized and included in the intention-to-treat analysis: 213 in the TcB group and 217 in the control group. In the TcB group, 104 (48.4%) had at least 1 blood sample taken for SB, versus 172 (79.3%) in the control group (difference 30.5%, 95% confidence interval 21.5–38.7, P < .001). The number of blood draws was significantly reduced by 38.5% (0.9 ± 1.1 vs 1.3 ± 1.0, difference –0.5, 95% confidence interval –0.7 to –0.3, P < .001). Peak of bilirubin value, indications for phototherapy, or exchange transfusion and hospitalization length were not different between groups.

CONCLUSIONS: The use of TcB in jaundiced neonates is feasible and safe, resulting in a reduction of more than one-third in blood draws.

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Ms van den Esker-Jonker conceptualized and designed the study, and revised the article; Ms den Boer carried out the data collection and the initial analyses on the maternity ward, and drafted the initial manuscript; Dr Pepping carried out the data collection and the initial analyses of the neonatal ward, and drafted the initial manuscript; Dr Bekhof designed the study, coordinated and supervised the process, critically reviewed the manuscript, and wrote the final draft as submitted; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered at www.clinicaltrials.gov (identifier NCT01622699).

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WHAT'S KNOWN ON THIS SUBJECT: The use

of transcutaneous bilirubinometry (TcB) in jaundiced newborns for screening of severe hyperbilirubinemia is valid and well investigated. Its use is advised in major international guidelines. However, TcB is not widely used yet, especially not in sick, hospitalized neonates.

WHAT THIS STUDY ADDS: This study shows that the use of TcB is feasible, safe, and leads to a reduction of one-third in blood draws in hospitalized neonates. These data can be helpful during decision-making about implementing TcB in pediatric wards.

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Active screening of newborns at risk for neonatal jaundice for severe hyperbilirubinemia is advised in major international guidelines.^{1–3} Visual assessment of neonatal jaundice is known to be unreliable^{2,4} and determination of serum bilirubin (SB) is, after the routine screening for inborn errors, the most frequent reason for blood draws in neonates.^{5,6} Although the use of transcutaneous bilirubin (TcB) measurement is a valid method for determination of the severity of jaundice and is used in increasing frequency, its use is still not widespread worldwide yet.⁷⁻⁹ In February 2016, we performed a telephonic review among most Dutch hospitals with neonatal wards (n = 37), which revealed that TcB was used in only 27% of these wards. Moreover in a Delphi study, the utility of TcB in jaundiced neonates was in the top 10 of most important research topics in neonatology.¹⁰ Possibly, a low confidence in bilirubinometry plays a role here, based on earlier studies using older nonvalid techniques.¹¹ One reason of nonapplication of TcB may be the assumption that in sick neonates TcB is less useful, because in these neonates blood sampling is often done for other indications and SB measurement is simultaneously measured. Furthermore, in lowincome countries, TcB is not widely applied, although this may be of great value due to feasibility of TcB in community settings with low resources.12,13

Since the 1980s, the use of a transcutaneous bilirubinometer has already been described to decrease blood draws and costs. However, quantitative data on the amount of reduction in blood draws from prospective studies are sparse.^{5–11,14,15} Most published data on the use of TcB originate from validation studies, comparing SB with TcB, by using a retrospective or observational study design in community settings or nurseries, in mostly relatively healthy (near) term populations.^{4–6,8,14–17} Recently, it has been shown that the use of TcB can be applied reliably in preterm infants with gestational age of 28 to 35 weeks as well,^{18,19} emerging the question of what reduction in blood draws can be achieved in this group of neonates?

This study aims to quantify the reduction in blood draws as a result of implementing a TcB in hospitalized jaundiced neonates from 32 weeks of gestational age, compared with visual assessment with subsequent blood sampling for determination of SB.

METHODS

Study Design

From February 2014 through April 2016, we conducted a randomized controlled trial, with an allocation ratio of 1:1, in the neonatal ward and the maternity ward of the Princess Amalia Children's Clinic of Isala, a large general teaching hospital in Zwolle, The Netherlands.

Patients

In the maternity–well neonates ward, accounting for ~3700 births each year, healthy neonates are nursed together with their mothers from 36 weeks' gestational age and birth weight >2200 g. Most neonates are discharged from the hospital with their mothers the same day, where the midwife takes care of further follow-up.

The population on the neonatal–sick neonates ward primarily consists of moderately preterm infants (32–35 weeks' gestational age), low birth weight infants (birth weight 1200– 1800 g), infants needing noninvasive respiratory support (nasal continuous positive airway pressure or supplemental oxygen through nasal cannula), and infants treated for neonatal hyperbilirubinemia, hypoglycemia, or (suspected) neonatal sepsis. Neonates needing mechanical ventilation or inotropic support are admitted to the NICU, as well as preterm neonates born at <32 weeks' gestational age or with birth weight <1200 g. The neonatalsick neonates ward receives ~500 admissions per year.

All hospitalized newborns with gestational age ≥32 weeks, older than 24 hours but younger than 8 days with a clinically observable jaundiced skin, were eligible for this study. Newborns were excluded in case of hemolytic disease of the newborn, clinical kernicterus, congenital anomaly on the sternum, earlier treatment with phototherapy, or previous blood sampling for SB.

Intervention

In the intervention group, sternal TcB (Air-Shields Jaundice Meter-103; Dräger Konica Minolta, Lubeck, Germany) was used, and in the control group, standard care was applied. In standard care, the decision to draw blood for SB was based on visual and clinical assessment by a physician. The need for phototherapy was based on the Dutch national guideline, which uses the nomograms as advocated by the American Academy of Pediatrics.² In every neonate with a TcB value <50 µmol/L below the applicable threshold for phototherapy, a blood sample was taken for SB measurement. The decision to start phototherapy was based on the SB value plotted in the international nomogram. The 50-µmol/L margin was applied to avoid false-negative TcB measurements, because of a known difference of TcB compared with SB.¹⁵ To safeguard against missing a neonate with significant hyperbilirubinemia, the attending physician could order a blood sample for SB at all times, despite normal values of TcB. We had no other safeguarding mechanism, such as routine screening of bilirubin in all hospitalized neonates, because standard screening of all newborns is not common practice in the

Netherlands and is not (yet) included in our national guideline, and our goal was to compare the intervention to the current standard practice.²⁰

Outcomes

Primary outcome was the number of blood samples taken for determination of SB, before the start of indicated photo- or exchange therapy. Secondary outcomes were the highest bilirubin value, age at the time of the first bilirubin measurement (TcB in intervention group or total serum bilirubin in control group), treatment with phototherapy or exchange transfusion, and length of hospital stay.

Sample Size Calculation

As we estimated the incidence of severe hyperbilirubinemia, and thus the effect of using TcB to be different in well infants on the maternity ward compared with sick neonates on a neonatal ward, exhibiting more risk factors for severe hyperbilirubinemia, we chose to perform subgroup analysis upfront and consequently used 2 different sample size calculations for the 2 different populations.

Before the start of this study, 75% of admitted neonates to our neonatal ward had at least 1 blood draw for determination of SB, compared with an estimated 20% of neonates on the maternity ward.⁵ We calculated a sample size of 164 patients for the neonatal ward and 438 patients for the maternity ward to be able to find a 30% reduction in blood draws,¹⁵ with a power of 80% ($1 - \beta$) and a significance level of 5% ($\alpha = 0.05$).

Randomization

When an attending nurse or physician recognized jaundice in a neonate, he or she asked permission from the parents/caretakers for participation in the study. After written informed consent was obtained from the parents or caretakers, eligible neonates were randomized by a computerized program, ensuring concealment of allocation. Randomization was stratified for gestational age, by using 3 stratification groups: \geq 32 and <34 weeks, \geq 34 and <38 weeks, \geq 38 weeks of gestational age, and was performed separately for the 2 wards. Given the nature of the intervention, blinding of the intervention was not possible.

Statistical Analysis

Continuous variables with normal distributions were analyzed with the Student's *t* test. When a non-normal distribution was found, the Mann-Whitney *U* test was used. For the dichotomous outcome measures, the χ^2 or Fisher's exact test was used. A *P* < .05 was considered significant. Data were analyzed by using SPSS version 23 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). We applied intent-to-treat analysis.

Study Approval

Written informed consent from the parents or caretakers was obtained before inclusion. The trial protocol and consent forms were approved by the hospital's local ethical committee (NL40354.075.12) and the trial was registered at clinicaltrials.gov (NCT01622699).

RESULTS

A total number of 534 jaundiced neonates were assessed for eligibility, of which 104 were excluded for various reasons (Fig 1); 430 jaundiced newborns were randomized and included in the intention-to-treat analysis: 254 from the maternity ward and 176 from the neonatal ward. Inclusion of eligible patients started in February 2014 and finished in June 2015 on the neonatal ward. Inclusion of eligible patients on the maternity ward was less than anticipated. For practical reasons, because of lack of available research personnel after a 2-year study period, inclusion of eligible

patients on the maternity ward was stopped, while not completing the calculated sample size of 438 patients, but only 58% (n = 254). Follow-up ended at discharge from our hospital. There was no loss to follow-up.

Baseline characteristics are presented in Table 1, showing no relevant differences between the intervention and control groups.

Primary outcomes are presented in Table 2. The number of blood draws per neonate in the TcB group was significantly reduced by 38.5%compared with control (mean ± SD: 0.9 ± 1.1 vs 1.3 ± 1.0 , difference -0.5(95% confidence interval [CI] -0.7 to -0.3), P < .001).

Secondary outcomes are presented in Table 3. We found no significant differences in secondary outcomes or adverse events between both groups, except for the age at the time of the first bilirubin measurement, which was 5 hours earlier in the intervention group (Table 3). We did not encounter clinical kernicterus, or were any of the participating patients treated with exchange transfusion. In the neonatal ward, the highest bilirubin value was slightly, but not clinically relevant higher in the TcB group compared with control. None of the measured SB values were extreme (\geq 425 µmol/L) or hazardous (\geq 512 µmol/L). Four neonates, however, had an initial SB value above exchange transfusion. In the neonatal ward, the 3 neonates with SB values above the exchange transfusion threshold were in the TcB group and were all very prematurely born (32 and 33 weeks' gestational age). The infant in the maternity ward with an SB value above exchange transfusion threshold, who was in the control group, had a gestational age of 37+6 weeks and a hematoma due to vacuum extraction. All 4 patients had values below exchange transfusion thresholds when exchange blood was available (typically after 2-4 hours), so no exchange therapy was applied.

TABLE 1 Baseline Characteristics of Included Patients

	Neona	Neonatal Ward		Well-Infant Nursery	
	Intervention, TcB, n = 86	Control, Visual Assessment, <i>n</i> = 90	Intervention, TcB, n = 127	Control, Visual Assessment, n = 127	
Boys, <i>n</i> (%)	49 (57.0)	50 (55.6)	61 (48.0)	69 (54.3)	
Gestational age, wk, mean (SD)	35 (2)	35 (2)	38 (2)	38 (2)	
Birth weight, g, mean (SD)	2491 (664)	2434 (499)	3190 (552)	3278 (580)	
Small for gestational age, <2 SD, n (%)	2 (2.3)	5 (5.6)	3 (2.4)	0 (0)	
Comorbidity, n (%)					
Gestational age <38 wk	79 (91.9)	80 (88.9)	50 (39.4)	49 (38.6)	
Asphyxia	2 (2.3)	0 (0)	1 (0.8)	0 (0)	
Blood group incompatibility	0 (0)	0 (0)	1 (0.8)	0 (0)	
Sepsis/meningitis	5 (5.8)	2 (2.2)	0 (0)	0 (0)	
Non-White, n (%)	4 (4.7)	6 (6.7)	11 (8.7)	10 (7.9)	



FIGURE 1

Participant flowchart. No loss to follow-up. *Main reasons: not meeting inclusion criteria (n = 35), could not be randomized due to logistic issues (weekends, holidays) (n = 23), declined to participate (n = 20), unknown (n = 13), Jaundice Meter-103 being out of order (n = 6), don't want to bother parents of sick neonates (n = 4), language barrier (n = 3). **Allocated to the intervention group, but did not receive intervention (n = 4).

Follow-up until 1 month after birth has been normal.

Agreement Between TcB and SB

We compared TcB with SB in 158 paired samples in patients in the intervention group with TcB above the threshold, in which case both TcB as well as SB were obtained, using a Bland Altman plot (Fig 2). The mean difference was 7.0 μmol/L (TcB minus SB), with limits of agreement of – 56.9 to 71.0 μmol/L.

DISCUSSION

This randomized controlled study showed that the use of TcB compared with visual assessment with subsequent determination of SB, results in a reduction of 38.5%

TABLE 2 Primary Outcomes

	Intervention, TcB	Control, Visual Assessment	Difference (95% CI)	Р
Total, n	213	217		
Neonates with minimal 1 SB sample, <i>n</i> (%)	104 (48.8)	172 (79.3)	-30.5 (-21.5 to -38.7)	<.001ª
Blood samples per patient before phototherapy, median (IQR)	0 (0-2)	1 (1–2)	-1.0 (-1.49 to -0.51)	<.001 ^b
Neonatal ward, <i>n</i>	86	90		
Neonates with minimal one SB sample, n (%)	61 (70.9)	87 (96.7)	-25.8 (-15.3 to -36.3)	<.001ª
Blood samples per patient before phototherapy, median (IQR)	1 (0—2)	2 (1–2)	-1.0 (-1.68 to -0.32)	.002 ^b
Maternity ward, n	127	127		
Neonates with minimal 1 SB sample, n (%)	43 (33.9)	85 (66.9)	-33.0 (-20.9 to -43.8)	<.001a
Blood samples per patient before phototherapy, median (IQR)	0 (0–1)	1 (0–1)	-1.0 (-1.00 to -1.00)	<.001 ^b

IQR, interquartile range.

 a P value calculated by χ^2 test.

 $^{\rm b}$ P value calculated by Mann-Whitney U test.

TABLE 3 Secondary Outcomes

	Intervention, TcB	Control, Visual Assessment	Difference (95% CI)	Р
Total, <i>n</i>	213	217		
Highest SB, μmol/L, mean (SD)	210 (46)	217 (65)	-6.6 (-21.4 to 8.3)	.386ª
Age at first TcB (intervention group) or first SB	53.9 (17.4)	59.2 (19.8)	-5.3 (-9.0 to -1.5)	.006ª
(control group), h, mean (SD)				
Phototherapy, n (%)	49 (23)	40 (14.4)	8.6% (-5.86 to 10.67)	.293 ^b
Severe SB, >342 μ mol/L, <i>n</i> (%)	2 (0.9)	7 (3.2)	2.3% (-7.79 to 0.61)	.310°
SB value above exchange transfusion threshold, n (%)	3 (1.4)	1 (0.5)	0.9% (-1.4 to -3.6)	.367°
Length of hospitalization, d, median (P25–P75)	6 (1-14)	7 (1–13)	NA	NA
Length of hospitalization on neonatal ward, d, ratio of geometric means (95% Cl)	1.0 (0.6–1.7)	NA	NA	.953ª
Neonatal ward, n	86	90		
Highest SB, μmol/L, mean (SD)	234 (53)	209 (59)	24.9 (-43.6 to 6.1)	.010ª
Age at first TcB (intervention group) or first SB (control group), h, mean (SD)	59.4 (19.9)	64.4 (21.0)	-5.0 (-11.2 to 1.2)	.110ª
Phototherapy, n (%)	31 (36.0)	25 (27.8)	8.2% (-5.4 to 21.6)	.310 ^b
Severe SB, >342 μmol/L, <i>n</i> (%)	2 (2.3)	2 (2.2)	0.1% (-5.7 to 6.1)	1.000 ^c
SB value above exchange transfusion threshold, n (%)	3 (3.5)	0 (0)	3.5% (-1.2 to 9.8)	.115°
Length of hospitalization, d, median (P25–P75)	11 (6-18)	12 (8–17)	NA	NA
Length of hospitalization on neonatal ward, d, ratio of geometric means (95% Cl)	1.0 (0.7–1.4)	NA	NA	.904ª
Maternity ward, n	127	127		
Highest SB, μmol/L, mean (SD)	222 (54)	204 (63)	18.1 (-4.2 to 40.5)	.110ª
Age at first TcB (intervention group) or first SB (control group), h, mean (SD)	50.3 (14.6)	53.8 (17.0)	-3.5 (-7.8 to 0.8)	.114ª
Phototherapy, n (%)	18 (14.2)	15 (11.8)	2.4% (-6.0 to 10.8)	.709 ^b
Severe SB, >342 μmol/L, <i>n</i> (%)	0 (0)	5 (3.9)	3.9% (0.2 to 8.9)	.167°
SB value above exchange transfusion threshold, n (%)	0 (0)	1 (0.8)	0.8% (-2.2 to 4.3)	.445°
Length of hospitalization on neonatal ward, d, median (P25–P75)	1 (1-1)	1 (1–2)	NA	NA
Length of hospitalization on neonatal ward, d, ratio of geometric means (95% Cl)	1.1 (0.7–1.6)	NA	NA	.638ª

The length of hospitalization in neonatal ward was log transformed before analysis because these variables were positively skewed. The effect of the intervention refers to the ratio of geometric means for the length of hospitalization in the neonatal ward. NA, not applicable.

^a *P* value calculated by independent samples *t* test.

 $^{\rm b}$ P value calculated by χ^2 test.

^c *P* value calculated by Fisher's exact test.

in blood draws, 21.1% when applied in a neonatal ward for sick neonates and 44.4% in the maternity ward. Obtaining a TcB is painless, quick, and easy, and it can be used as many times as desired, by different health care professionals without blooddrawing skills. TcB can be safely applied in hospitalized neonates, including medium- and high-care settings, as we found no difference in adverse effects, such as missed



FIGURE 2

Bland Altman plot, comparing TcB with SB. Mean difference 7.0 μ mol/L; 95% limits of agreement: lower limit –56.9 μ mol/L, upper limit 71.0. Clinical margins: 50 μ mol/L and –50 μ mol/L.

kernicterus, extreme or hazardous hyperbilirubinemia, or duration of hospitalization.

Our results confirm the results in earlier literature on this topic, reporting 20% to 50% reduction when using a transcutaneous device.^{6,15} Our study differed from previous reports because we included patients from 32 weeks' gestational age and sick neonates from a medium- to high-care neonatal ward, whereas most other studies included only healthy neonates from 35 weeks of gestational age.

The cost-effectiveness of TcB is difficult to generalize because the costs of SB measurements vary greatly between countries and even between hospitals within a country. Few studies suggest the cost of a TcB device is offset by the decrease in SB measurements.²¹ The quantitative data in this report can help other neonatal or maternity wards calculate the cost-benefit of TcB on their own ward. The main strength of our study is the design as a randomized controlled trial. Although many studies addressing various aspects of TcB devices have been reported, to our knowledge, this is the first randomized controlled trial in a Western population quantifying the effects of implementation of TcB in both a neonatal ward and a maternity ward setting.

A weakness of our study is that we had to stop the inclusion of eligible patients on the maternity ward after having completed only 58% (n = 254) of the calculated sample size of 438 patients. This was for practical reasons, because of lack of available research personnel after a 2-year study period. Before the start of the study we had expected a larger number of eligible neonates on this maternity ward, based on assumptions we made based on available literature and our delivery numbers, which might not have been correct. Because the results of this analysis demonstrate an effect

with clinically as well as statistically relevant 95% CIs, we think our study population of 254 patients is still sufficiently large for solid conclusions. Therefore, we assume the risk of a type 2 error to be negligible.

Another weakness is the lack of blinding of the treating health professionals. Given the nature of the intervention, blinding of the intervention was not possible. This implies that bias might have occurred in the control group, where the attending physician decided, based on visual assessment, whether an SB was ordered or not. During the study period, we had at least 35 different health professionals (pediatricians, nurse practitioners, and residents) working on the maternity and neonatal wards. Differences in the clinical assessment as well as individual differences in the threshold to order an SB may have existed. However, we think that this study design best reflects daily clinical practice where differences between health professionals' judgments can never be completely ruled out. Moreover, because most of the newborns in the control (ie, visual assessment) group (79.3%) had blood sample taken for SB, we do not think the bias has significantly influenced our results, nor our conclusion that TcB is safe and useful in hospitalized neonates. The main importance of this bias is that in situations in which standard screening of SB is applied, independent of visual assessment, the reduction in blood samples will be even larger.

We hope these study results prevent further unnecessary blood draws in neonates through the use of TcB. Further reduction in blood draws and costs may be achieved when TcB can be reliably applied during and after phototherapy, an application that needs further investigation, before it can be recommended in clinical practice.²²

CONCLUSIONS

This study shows that implementation of TcB reduces blood sampling by 38.4%, compared with visual assessment; without increasing the risk of missing neonates with hazardous hyperbilirubinemia. We advise the use of TcB in hospitalized jaundiced newborns.

ABBREVIATIONS

CI: confidence interval SB: serum bilirubin TcB: transcutaneous bilirubin

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