Development and Evaluation of a Smartphone Camera Method for Transcutaneous Bilirubin Measurements

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Assessment of a medical technology

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Abstract

Introduction

Worldwide, neonatal hyperbilirubinemia remains a common cause of readmission to the healthcare system, as it may cause kernicterus at high levels. This condition is treatable, why an easy and accessible screening tool, which enables self-measurement of bilirubin, is valuable and advantageous. However, such device is not yet available. Hence, we aim to examine if the embedded camera on a smartphone can be a reliable tool in order to screen and monitor for neonatal hyperbilirubinemia.

Methods

A total of 49 Caucasian neonates admitted to Aalborg University Hospital were randomly selected for the study between 15th of July and the 3rd of December 2015. Three methods were evaluated using an iPhone 6 for the assessment. In the first method, we simply used the camera on the smartphone to apply moderate pressure on the glabella of each neonate while recording a video or taking a picture. Secondly, we used a Dermatoscope (DermaLite Pro II) attached to the iPhone to obtain each video. Thirdly, we applied a Wratten No. 11 Colour Filter between the DermaLite Pro II and the camera on the iPhone 6. A transcutaneous bilirubinometer (TcB) or a total serum bilirubin measurement was used as reference. The red, green and blue colour intensities of each video were analysed and correlated to the respective bilirubin reference values.

Results

No significant correlation between the iPhone 6 analysis and reference bilirubin levels using the first and second method was observed (Pearson´s correlation coefficient; red channel 0.05 and -0.38; green channel -0.03 and -0.05; blue channel -0.11 and 0.01). However, method three revealed a significant negative Pearson´s correlation coefficient of 0.61 (p = 0.015) between the blue channel intensities and the TcB with a coefficient of variance of 22.5 %.

Conclusion

The presented methods demonstrate differential results. Method three did, however, indicate a proof of concept and therefore we believe that a combination of

standardised light, even pressure and a filter excluding the reflectance of haemoglobin along with further improvements and studies, can be useful in the screening process of neonatal hyperbilirubinemia.

Kan et smartphone kamera anvendes som et redskab til transkutan bilirubin måling?

Resumé

Introduktion

Neonatal hyperbilirubinæmi er en persisterende problemstilling verden over. Denne tilstand kan i værste tilfælde forårsage kernikterus og giver derfor anledning til utallige genindlæggelser. Heldigvis kan neonatal ikterus behandles, hvorfor et nemt og tilgængeligt redskab, som gør det muligt for forældre selv at screene og monitorere for forhøjede bilirubin værdier i hjemmet, er fordelagtig. Desværre er sådan et redskab endnu ikke tilgængeligt.

Smartphones bliver brugt af 1.6 billioner mennesker verden over og samtidig er der tale om eksponentiel vækst indenfor teknologien. Derfor er dette område en oplagt mulighed for at udvikle et sådan redskab. Dette studie har til formål at undersøge, om det indbyggede kamera i en smartphone er et valid redskab til måling og monitorering af neonatal ikterus, således at dette kan være medvirkende til, at genindlæggelser og unødvendig smerte og bekymring, hos børnene og deres forældre, kan reduceres.

Metode

I alt blev 49 nyfødte kaukasiere tilfældigt udvalgt til studiet. Disse var alle indlagt på Aalborg Universitetshospital i perioden fra 15. juli til den 3. december 2015.

Vi undersøgte tre metoder med en iPhone 6. Ved den første metode brugte vi udelukkende kameraet til at påføre et moderat tryk på panden af de nyfødte, mens vi optog en video eller tog et billede. Ved den anden metode anvendte vi en DermaLite Pro II til at påføre trykket med, og ved den sidste og tredje metode, anvendte vi et Wratten No. 11 farvefilter mellem kameraet og DermaLite Pro II.

Et transkutan bilirubinometer (TcB) eller total serum bilirubin analyseret ved diazoreaktion eller via Acid Base Laboratory (ABL) test blev anvendt som referencemetode.
De røde, grønne og blå (RGB) farveintensiteter af alt data blev analyseret via en udarbejdet algoritme og korreleret med deres respektive bilirubin referenceværdi.

Resultater

Af alle inkluderede børn var 51 % piger og den gennemsnitlige gestationsalder og fødselsvægt var henholdsvis 38 ± 2 uger og 3248 ± 694 g. Alt data var i gennemsnit indsamlet 4,5 dag efter fødslen og rangerende fra 2 til 16 dage. Værdierne for det TcB lå mellem 51 og 303 µmol/L.
Der fandtes ingen signifikant korrelation mellem metode et og to og bilirubin referenceværdierne, hvad enten målingerne var sammenlignet med total serum bilirubin eller bilirubinometeret. Pearson´s korrelations koefficient mellem RGB intensiteter og TcB var 0,05 og -0,38 for den røde kanal, -0,03 og -0,05 for den grønne kanal og -0,11 og 0,01 for den blå kanal i henholdsvis metode 1 og 2.
I metode to observeredes der en mindre sammenhæng mellem den røde kanals intensiteter og TcB ($r = -0.38$), men den var dog ikke signifikant ($p = 0.12$), og den var desuden baseret på få målinger (n=18).
Dog, var der en signifikant negativ Pearson´s korrelations koefficient mellem den blå kanal i metode tre og bilirubin på 0,61 (p = 0,015) med en variationskoefficient på 22,5 %.

Konklusion

Dette studie viser tvetydige resultater. Metode tre indikerer dog et ”proof of concept”, som teoretisk kan verificeres grundet den blå farves komplementaritet til den gullig-orange farve, som visuelt kan observeres i barnets hud ved neonatal ikterus. Derfor kan man forestille sig, at en kombination af standardiseret lys, jævnt tryk og et filter som ekskluderer refleksionen fra hæmoglobin, samt yderligere forbedringer og studier, kan gøre metoden så valid, at den i fremtiden kan anvendes som screening for neonatal ikterus.

Introduction

Worldwide, neonatal hyperbilirubinemia remains a common cause of readmission in the healthcare system, as unconjugated bilirubin may potentially, at high levels, cause acute and chronic bilirubin encephalopathy (kernicterus) (1,2). Fortunately, this condition is treatable by means of phototherapy or in rare cases exchange transfusion (3). Thus, it is vital that newborns are observed for hyperbilirubinemia and screened accordingly if jaundice is suspected. However, bilirubin in term infants peaks within the first three to five days after birth, where most infants have already been discharged. Thus, it would be favourable to develop an easy and accessible tool that enables self-measurement of bilirubin outside the hospital (3).

Accepted methods for bilirubin measurement

Various methods for assessing bilirubin levels in neonates are available such as invasive blood samples, non-invasive transcutaneous bilirubinometers (TcB) and visual assessment.

Total serum bilirubin (TSB) measurement remains the gold standard, as contradictory studies question the validity of non-invasive technologies (4–7). Hence, TcB remains a supplement tool that reduces the frequency of TSB measurements and the costs related to it (8,9). As a consequence, TSB remains one of the most frequently performed tests on neonates resulting in costly and invasive blood samples with a risk of infection (10), pain (11) and parental stress (12).

Despite the fact that TcBs have obvious advantages as Point-of-care testing (POCT) in respect to time, pain and adverse effect, the TcBs are still too expensive to use for home monitoring (5).

Hence, subjective visual assessment of the skin colour is often performed as the first method of evaluation as guidance for the parents and health care staff. By applying pressure on the neonatal forehead with the finger, the blood (red haemoglobin) is removed from the surface to reveal the intensity of yellowing of the skin. However, this method is not even reliable when performed by experienced healthcare professionals (13).

A more standardised method is available, called icterometer, which is primarily used in countries with limited resources. This tool enables the user to blanch the skin with a

transparent plastic strip in order to grade the bilirubin into five levels utilising the human eye, but this tool is neither valid for screening (14).
Thus, no easy, accessible, inexpensive and reliable method is yet available for outpatient monitoring for neonatal jaundice.

Properties of normal and jaundiced neonatal skin

The layers of the neonatal skin are fairly homogenous compared to adults (15). In the skin, several chromophores are present such as haemoglobin, bilirubin and melanin, which each absorb light at different wavelengths (Figure 1). The appearance of the skin varies in accordance to several parameters such as postnatal age, hydration status, epidermal melanin content and cutaneous blood content (5,15–17).
In neonatal jaundice, excess bilirubin in the blood stream diffuses into tissues, leading to yellowing of the skin. The yellowing progresses in the cephalocaudal direction and fades in the opposite direction (18). With this knowledge in mind, the forehead makes a suitable place for detecting bilirubin level transcutaneously, as this location has the highest value at all times and at the same time it is convenient for testing (5,17).

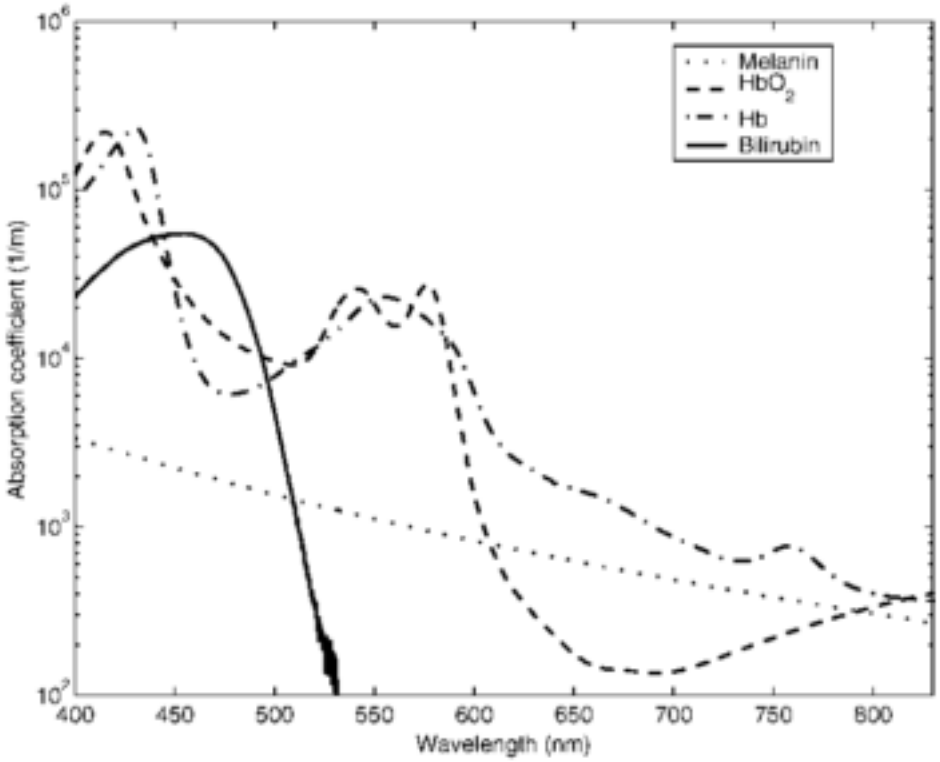

Figure 1 - Chromophores in the human skin. The absorption spectrum of haemoglobin (Hb), oxyhaemoglobin (Hb02), bilirubin and melanin. The figure is from Randeberg LL et al. (17).

Mobile health technology

During the past decade, the emergence of ubiquitous smartphones with powerful processors, high-resolution cameras and communication capabilities have increased substantially (19). With over 1.91 billion smartphone users worldwide (28), these tools reveal new possibilities for facilitating "personalised medicine", which enables tracking of changes over time, improving patient empowerment and self-management with home-based tests and tools (19–24). Moreover, smartphones have shown to be a unique tool in developing countries, as they are inexpensive, easy and accessible. Consequently, smartphone-based health related tools such as pulsoximeters and microscopes have already been developed (19,25–27).

This trend has also gained ground in the field of neonatal jaundice, where an accessible screening method for bilirubin may potentially reduce the number of readmissions caused by the suspicion of jaundice and even decrease the incidence of kernicterus worldwide.

BiliCam is the first of its kind, which uses the built-in camera to assess the yellowing of the skin with a colour calibration card (28). This method has not yet been published in any scientific journals, but it reveals a correlation with TSB of 0.82 to 0.85 with several limitations such as unexplained outliers. Two other tools have been described, but none of these have yet proved their accuracy (27,29). Hence, this renders new possibilities of improving and exploiting this field of technique even further.

We hypothesized that the embedded camera on the smartphone can be used as an intelligent icterometer. Thereby becoming a reliable tool in order to screen and monitor for neonatal hyperbilirubinemia and potentially be an easy and accessible adjunct to the current gold standard. Also, this method would potentially enable the parents to perform home monitoring of the newborns, even at remote areas and limited resource countries, consequently decreasing readmissions to the hospitals caused by the suspicion of neonatal hyperbilirubinemia.

Materials and Methods

Subjects

A total of 49 Caucasian neonates admitted to Aalborg University Hospital between 15th of July and the 3rd of December 2015 were randomly selected for the study. We

only included subjects that were clinically assessed with jaundice by nurses or doctors. We excluded neonates that were being treated with phototherapy or had bruising, skin infections or purpura present on the forehead. All demographic details such as gestational age and birth weight were obtained from hospital records. The Ethics Committee in the Region of North stated that no ethical approval was necessary. Still, verbal consent from all parents was obtained before initiating data collection. No parents refused to participate.

Experimental protocol

Technical specification

We evaluated three methods for the assessment of neonatal jaundice. All experimental measurements were obtained on the glabella of the forehead with an iPhone 6 facing in a downward direction. They were performed with as little variability as possible when the babies were in a quiet state.

We used the same iPhone 6 (Apple, Inc., Cupertino, CA, USA) as the primary tool. The iPhone 6 has an 8 megapixels iSight-camera with a 1.5 µ pixels, which is able to record slow motion videos taking 240 pictures per second (30). The smartphone was thoroughly disinfected before and after each measurement to avoid any contamination.

Reference tools

As a reference, we used the BiliChek bilirubinometer (Philips Respironics, Koninklijke Philips Electronics NV, Eindhoven, the Netherlands) and/or blood sampling, if available, to minimize any unnecessary harm to the patients.

BiliChek uses an optical multiwavelength spectral reflectance technique in order to detect the bilirubin level and has proved to be fairly accurate (r = 0.83 to 0.97 compared with TSB) (3,29). A single investigator obtained all TcB reference values immediately after the explorative measurements. They were performed as recommended with an initial calibration and five repeated measurements. A mean bilirubin level of these repetitions was calculated and used as final data.

TSB was obtained by heel puncture and analysed with the diazo reaction method or via the Acid Base Laboratory test (ABL). The health care staff took the TSB within two hours from the experimental measurements.

Methods of evaluation

First method

With the embedded camera on the iPhone 6, the investigator applied moderate pressure to the glabella in order to remove the haemoglobin from the superficial skin. Simultaneously, videos and pictures were obtained with flash. Attention was paid to keep a constant pressure on the skin during measurements.

This method was performed on all 49 subjects. An example of how it was performed along with an example of an outcome is illustrated in figure 2.

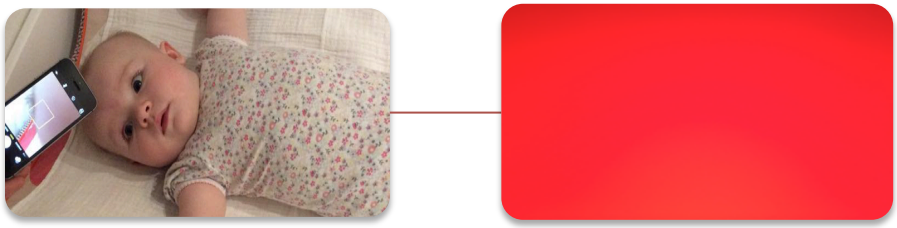

Figure 2 - Method one and an example of an outcome.

Second method

A DermaLite Pro II is a dermatoscope used to enhance visualization of the skin for dermatologists (31). We improved the first experiment by applying a tool in front of the camera in order to standardise the light and increase the surface area of which the pressure was applied. During measurements attention was paid to maintain a constant pressure on the skin. Method two was obtained on 18 subjects. An example of how it was performed along with an example of an outcome is illustrated in figure 3.

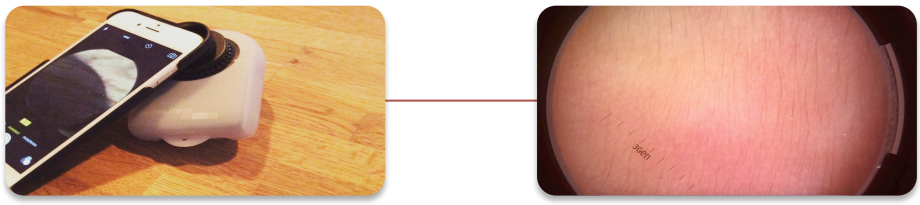

Figure 3 - Method two and an example of an outcome.

Third method

The only difference between method two and three is that we applied a yellowish green Wratten No. 11 Colour Filter between the smartphone camera and the DermaLite Pro II. This colour filter has a

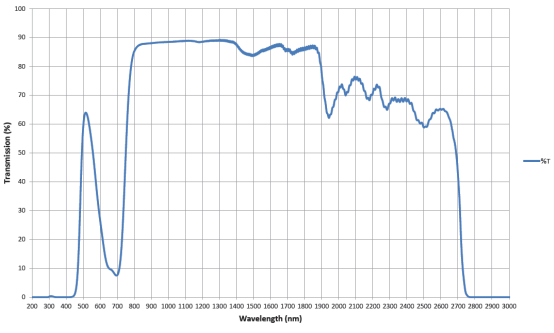

Figure 4 - The Wratten No. 11 Colour Filter and its transmission of wavelenghts in % (32).

wavelength cut-on, peak, and cut-off of 483, 516 and 589, respectively (Figure 4) (32).

Haemoglobin is the predominant chromophore in the skin and overlaps bilirubin in absorbance spectrum in the skin, which makes bilirubin difficult to detect transcutaneously (Figure 1). Therefore, the Wratten Colour Filter ought to reduce the reflectance coming from haemoglobin and thereby enabling wavelengths from bilirubin to be detected. Method three was obtained on 15 subjects. An example of how method three was performed along with an example of an outcome is illustrated in figure 5.

Figure 5 - Method three and an example of an outcome.

Data analysis

All data was either obtained as pictures (only method one) or slow motion videos. Subsequently, a review to exclude any inapplicable data was performed and only one measurement per infant was included in the final analysis, based on best visual quality.

A quantitative analysis of all videos was performed with an automatic custom-coded algorithm.

For each method we assessed five variables, if available:

1) An average red, green and blue (RGB) channel intensity was calculated from a selected area throughout the videos and subsequently, a Pearson´s correlation coefficient of the relationship between the respective channel intensities and TSB or TcB was deduced for each method.

2) A coefficient of variation (CV) of all videos was computed.

3) The average intensity of the RGB channels was extracted from each selected frame of the video and CVs were calculated.

4) Explorative measurements were repeated at least twice within an interval of 20 seconds to one minute to calculate a CV of duplicate measurements with an equation shown in figure 6.

$$SD = \sqrt{\frac{\sum d^2}{2n}}$$

Figure 6 - The equation used to determine the standard deviation of duplicates. SD: standard deviation; D= difference; N= number of duplicates

5) If subjects were admitted several days, measurements were obtained repeatedly during this period, visualized in a scatter plot of the interpersonal variation.
The main steps towards deducing results from the videos are present in a flowchart in figure 7.
For picture analysis in method one, a manually selected area of each digitalised picture was analysed with ImageJ (1.49v, National Institute of Health, USA).
We defined RGB colour intensity of 255 – (R, G and B).

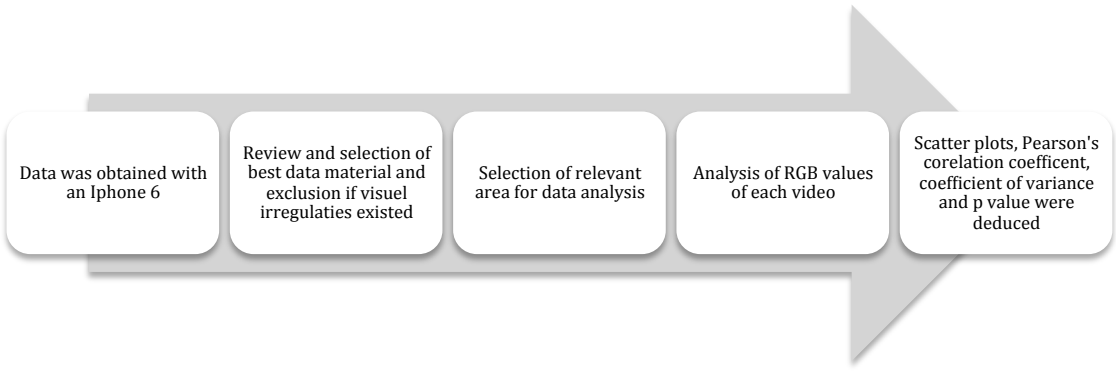

Figure 7 - Flowchart of each step performed during data collection and analysis.

Statistics

Data analysis was performed in MATLAB R2015a 8.5.0 (MathWorks Inc., Natick, MA, USA). Calculations were completed using SPSS 15.2 for MAC (SPSS, Chicago, IL, USA) and Excel 2010 (Microsoft, Redmond, WA, USA).
A p value of ≤ 0.05 was considered statistically significant.

Results

A total of 49 Caucasian newborns were enrolled in the study with 51 % being girls. The mean gestational age of the study population was 38 weeks (standard deviation (SD) ± 2 weeks), ranging from 33 to 41 weeks. The mean birth weight was 3248 ± 694 g, ranging from 1700 to 4420 g. All measurements were taken on average 4.5 days postnatally, ranging from 2 to 16 days. The TcB values ranged from 51 to 303 µmol/L. All demographic details are shown in table 1.

Parameter (*n*=49)	
Gestational age (weeks)	
Mean ± SD	38 ± 2
Range	33+3 – 41+5
Birth weight (g)	
Mean ± SD	3248 ± 694
Range	1700 - 4420
Birth length (cm)	
Mean ± SD	50 ± 2.7
Range	44 - 55
Head circumference (cm)	
Mean ± SD	34.6 ± 2.0
Range	31 - 38
Sex	
Boy	24 (49.0)
Girl	25 (51.0)
BiliChek reference levels (*µ*mol/liter)	
Mean ± SD	194.7 ± 56.6
Range	51 – 303

Table 1 - Demographics and characteristics of the study population. Data are shown as the mean ± standard deviation or in percentage (%).

First method (iPhone 6 only, Appendix A)

1) We obtained both videos and pictures during data collection, but neither of them showed any significant correlation with TcB with Pearson´s correlation coefficients of -0.24, 0.03 and -0.11 for the RGB channels in the videos, respectively (Table 2, Appendix 1.1 and 1.4-5). None of the results were statistically significant.

2) The RGB intensities of all videos had CVs of 1.19 %, 79.03 % and 4.97 %.

3) The average CVs of the individual videos were 0.17 %, 17.19 % and 3.02 % for the RGB intensities.

4) A duplicate determination of the pictures showed CVs of 5.30 %, 152.72 % and 2.00 % for RGB values.

5) We obtained data from five subjects within several days, but this was equivocal (Appendix 1.6).

No substantial improvement was observed when the RGB values were correlated with TSB instead of TcB reference values (Appendix 1.2).

Method 1 – Videos *(n=49)*					
Channel	**Reference tool**	**CV of all data (%)**	**CV of videos (%)**	**Pearson's correlation coefficient**	***p* value**
Red	TcB	1.19	0.17	-0.24	0.12
	TSB			0.34	0.21
Green	TcB	79.03	17.19	0.03	0.84
	TSB			-0.06	0.84
Blue	TcB	4.97	3.02	-0.11	0.51
	TSB			0.44	0.98

Table 2 - An overview of results in method 1. TcB: Transcutaneous bilirubinometer, CV: Coefficient of Variance

Second method (iPhone with DermaLite Pro II, Appendix B)

1) The Pearson´s correlation coefficients were -0.38, -0.05 and 0.01 for the RGB channels and TcB, respectively (Table 3, Appendix 2.2). None of which was statistically significant. A certain tendency of decreasing intensity of the red channel with rising bilirubin levels was observed (Figure 8 and Appendix 2.1).

2) The CVs of all videos were 8.72 %, 11.93 % and 19.84 % for the RGB values.

3) The average CVs for the individual videos were 4.38 %, 5.51 % and 6.28 % for the RGB intensities.

5) The scatter plot illustrating the interpersonal variation showed differential slopes Figure 9 (Appendix 2.2).

Method 2 *(n=18)*					
Channel	**Reference tool**	**CV of all data (%)**	**CV of videos (%)**	**Pearson's correlation coefficient**	***p* value**
Red	TcB	8.72	4.38	-0.38	0.12
Green	TcB	11.93	5.51	-0.05	0.85
Blue	TcB	19.84	6.28	0.01	0.97

Table 3 - An overview of results in method 2. TcB: Transcutaneous bilirubinometer, CV: Coefficient of Variance.

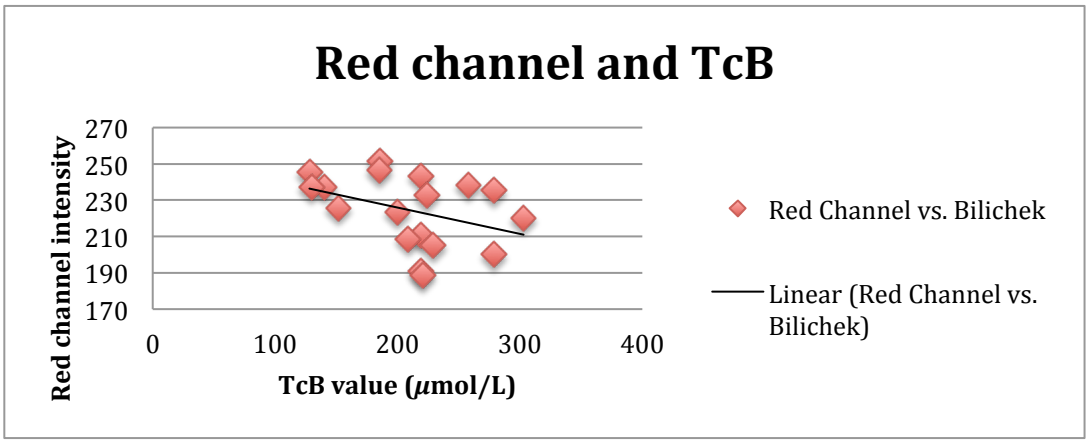

Figure 8 – Method two - The red channel intensities and its correlation with bilirubin levels (TcB).

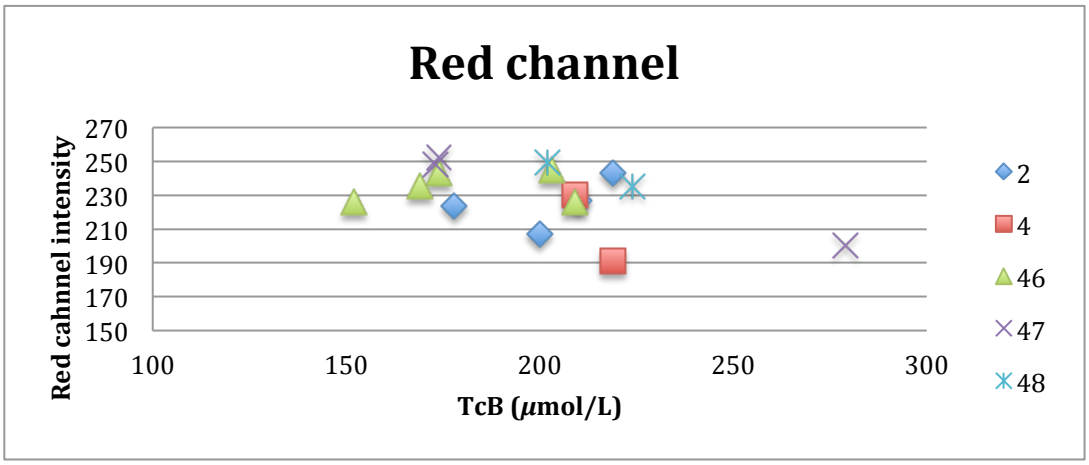

Figure 9 – Method two - The red channel intensities and its correlation with bilirubin levels (TcB) within several days on the same subjects.

Third method (iPhone with DermaLite Pro II and Wratten colour filter, Appendix C)

1) The Pearson's correlation coefficients between method three and TcB were 0.05, -0.03 and -0.61 for the RGB channels respectively (p = 0.89, 0.9 and 0.02) (Table 4). Decreasing intensity of the blue channel correlated relatively well with increasing TcB values and was statistically significant (p = 0.02) (Figure 10, Appendix 3.1).

2) CVs were calculated at 9.51 %, 1.17 % and 22.46 % for the RGB values.

3) The average CVs for the individual frames of the videos were 1.0 %, 0.05 % and 1.31 %.

4) The determination of duplicates revealed CVs of 4.01 %, 23.00 % and 3.53 %.

5) As depicted in figure 11 a certain variation was visualised when observing subjects within several days (Appendix 3.2).

Method 3 *(n=15)*						
Channel	**Reference tool**	**CV of all data (%)**	**CV of videos (%)**	**CV of duplicates (%)**	**Pearson's correlation coefficient**	***p* value**
Red	TcB	9.51	1.00	4.01	0.05	0.89
Green	TcB	1.17	0.05	23.0	-0.03	0.9
Blue	TcB	22.46	1.31	3.53	-0.61	0.02

Method 3 - An overview of results in method three. TcB: Transcutaneous bilirubinometers, CV: Coefficient of Variance

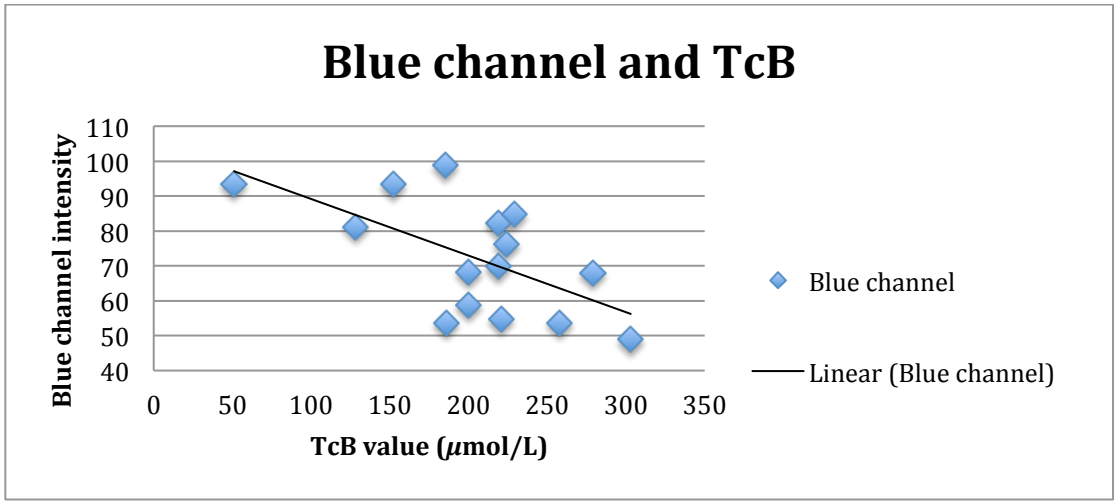

Figure 10 – Method three - The blue channel intensities and its correlation with bilirubin levels (TcB).

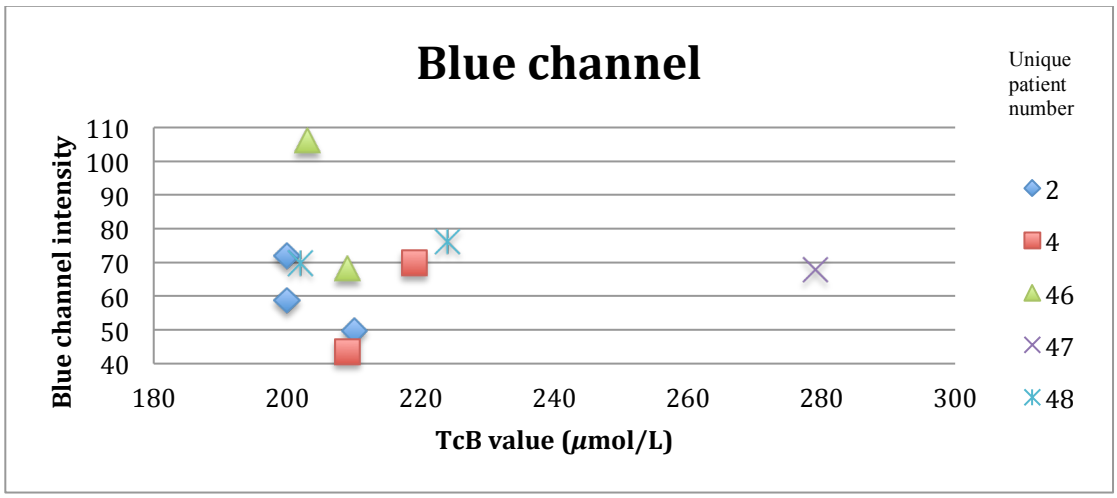

Figure 11 – Method three - The blue channel intensities and its correlation with bilirubin levels (TcB) within several days on the same subjects.

Discussion

Over half of the newborns acquire neonatal jaundice, all potentially at risk of kernicterus (27). At the same time, hospital admissions after birth are decreased considerably, which has drawn attention to the importance of identifying an accessible and inexpensive tool for detection and screening of neonatal hyperbilirubinemia. Therefore, with the exponential growth of technology, this tool serves as a perfect match to potentially overcome and reduce this issue.

We aimed to develop a technique, where no attachment to the smartphone was required, representing the first method of evaluation. Unfortunately, we were unable to reach this objective, as no significant correlations between the RGB intensities and TSB or TcB values were found. All things considered, this method might have too many influences from e.g. chromophores in the skin and light conditions as mentioned in the introduction, which makes method one too unpredictable to become a reliable medical device.

In method two a tendency of decreasing red channel intensities with increasing bilirubin levels was observed, but with a statistically insignificant p value and a SD of $\pm 19.57\ \mu mol/L$. Furthermore, the scatter plots where five subjects were included in the data collection within several days, neither corresponded to the observed tendencies. This indicates that this relation might be due to coincidences caused by e.g. a small sample size and unidentified variations in the study population, making method two unfeasible for further research within this field.

In method three we observed a significant correlation between decreasing blue intensities and rising bilirubin values. In theory, we can explain this by the fact that the Wratten No. 11 Colour Filter excludes wavelengths from the high amounts of haemoglobin in the skin, thereby revealing the changes in bilirubin concentration to a greater extent. Furthermore, it is well known that blue-violet and yellow-orange colours are complementary, which explains decreasing intensities of the blue colour channel when the yellow intensity ascends (33).

The Pearson´s correlation coefficient only reaches 0.61 and thereby this method does not reach an acceptable level of validity to substitute the current TcBs neither TSBs. Despite the fact that this tendency is significant, we must not elude the fact that this might also be caused by coincidences. This assumption is partly confirmed in the scatter plots, where only three set of measurements out of five have a decreasing inclination (Figure 11). However, this might also be caused by the relatively high SD

at 15 - 18 μmol/L of the TcB along with 16.25 in the present method (43).
The current tool used in method three also entails some disadvantages, as the surface on the DermaLite Pro II is too wide in comparison to the glabella of the neonates. Therefore, it was difficult to maintain a constant pressure, and we were compelled to choose the area of analysis on each video manually. This may partially explain the relatively high SD of the entire data set, but on the other hand, the CV of duplicates and the individual frames of the videos revealed that the intensity of the blue channel was rather constant.
Unfortunately, the presented methods in this study were not able to reveal any technique that reached an acceptable level of validity to become a future bilirubin measurement tool, but the results were, however, able to indicate a proof of concept in method three.

Limitations
Several limitations to this study exist.
We presented a rather small sample size with only Caucasian newborns, which made this study non-representative of the entire study population.
Furthermore, due to the small number of included subjects, our results would potentially be more susceptible to outliers. This was our main incentive to review all data before performing the final analysis. Moreover, scatter plots for each method were composed with the purpose of identifying and explain the cause of any outliers. Unfortunately, the present study had too many outliers to verify exclusion. The inventors of BiliCam had a similar experience, but they were, however, able to explain the reason in some cases by their inclusion of non-white subjects (28).
We compared the data with both the TcB and TSB, if available, at data collection. However, the use of TcB as the primary reference value can be questioned due to its varying SD and correlation with the TSB. One study indicates that the TcB increasingly underestimates TSB (8). This issue has also been addressed in similar studies, where they chose the TSB as the primary reference tool (15). Therefore, if this study should be refined, it will be relevant to set up both tools for reference.
Moreover, a transcutaneous method involves several disadvantages, as changes in the superficial skin may substantially affect the results as many influences are present as mentioned in the introduction. This assumption was acknowledged by other studies, which have discovered some influential outcomes by testing transcutaneous tools on

e.g. subjects with high melanin content, gestational age, postnatal age and respiratory distress syndrome (11,43). None of these factors were considered in the present study, except the fact that subjects with any obvious visually abnormality were excluded. We used an iPhone 6 as the tool of evaluation. Significant differences between each individual device, model and platform exist (34). We chose the newest available Apple smartphone, as this is the most predominant device in Denmark. However, this is not applicable for the rest of the world, were Android smartphones are prevailing the market (35). These statistics especially apply for resource limited areas, where a bilirubin detection tool would especially make a remarkable difference. Hence, studies including smartphone technology would benefit from testing all methods on different devices, models and platforms.

Perspectives

Future studies should include a better tool for data collection, a more diverse and representative study population, with both TcB and TSB as reference tools being tested on the majority of available smartphones.

If these studies demonstrate positive outcomes, that reached the validity of the current accepted methods, we envision that a development of a connecting algorithm would advance the results substantially. An algorithm would facilitate screening for inapplicable data, thoroughly data analysis, continuous improvements of the algorithm based on interpersonal results and communication between users and healthcare facilities (36). If the tool can connect to health care facilities and notify them of any adverse outcomes without any interpersonal communication, the health care staff can take immediate action and thereby potentially reduce the risk of kernicterus and the cost related to it.

Furthermore, a connection to the internet would provide an opportunity to combine the algorithm with intelligent software, improving each result continuously. The intelligent software enables data to be put into context with other relevant patient data (26). Within the field of neonatal hyperbilirubinemia, relevant patient data can be gestational age, postnatal age, skin colour and risk factors such as cephalic haematoma and diabetic fetopathy (8,37). The parents can type in any relevant data on their smartphones and simultaneously sent off the data, which the algorithm along with the intelligent software would analyse together and thereby increase the chances of providing a valid and clinical relevant result (11,37,38).

In the present study, we used the intensity of RGB colour intensities, as this is commonly known for videos and picture analysis. This study, would, however, potentially benefit from using more detailed colour code methods. Another study by Li Shen et al. is addressing this limitation and states that RGB codes are insensitive and application specific, and, therefore, it is not able to generate any useful results (34). They recommend and present promising result by converting RGB to International Commission on Illumination (CIE) colour space (34), which may also be relevant for this study in the future. Furthermore, opportunities to use spectrophotometry, similarly to BiliChek, with a smartphone have been established (5). This may pave the way for new possibilities of a more valid tool for neonatal jaundice, but to our knowledge, no useful method is yet available for testing (19).
As a supplement to the present data analysis, we were able to obtain pictures from six subjects with appertaining available haemoglobin levels analysed with an ABL. This rather small sample size did, however, reveal a negative highly significant Pearsons´s correlation coefficient between the green channel intensity and haemoglobin of 0.98 ($p = 0.001$, Appendix D). Previous studies have observed this relation and similarly found a correlation. Two smartphone tools for the detection of haemoglobin have even been developed, but no medical device approval or evidence is yet available (40,41,42).

Conclusion

The results of the present study are equivocal. However, method three did indicate a proof of concept. Therefore, we envision that a combination of standardised light, even pressure and a filter excluding the wavelengths of haemoglobin along with further improvements and research would substantially validate this method in order to become as a useful and reliable tool in the screening process of neonatal hyperbilirubinemia.

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