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Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns (Protocol)

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[Diagnostic Test Accuracy Protocol]

Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns

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ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

- To determine the diagnostic accuracy of TcB as:

i) a diagnostic test for hyperbilirubinaemia in newborns suspected to have hyperbilirubinaemia on visual inspection;

ii) a diagnostic test for monitoring bilirubin levels in newborns receiving treatment (e.g. phototherapy) for hyperbilirubinaemia.

1. a diagnostic test for hyperbilirubinaemia in newborns suspected to have hyperbilirubinaemia on visual inspection;
2. a diagnostic test for monitoring bilirubin levels in newborns receiving treatment (e.g. phototherapy) for hyperbilirubinaemia.

- To determine whether the gestational age, postnatal age, body weight, race and site of TcB measurement have any influence on the accuracy of TcB measurement for hyperbilirubinaemia in newborns.

BACKGROUND

Target condition being diagnosed

Hyperbilirubinaemia is a term used to describe excess of bilirubin in the blood. In newborns, hyperbilirubinaemia becomes clinically apparent as jaundice, a yellow colouration of the skin and sclera (Woodgate 2015). Hyperbilirubinaemia is very common in both term and preterm newborn infants (occurring in about 60% of newborns) and results from a predisposition to the production of bilirubin and their limited ability to excrete it (Lauer 2011). Most cases of newborn jaundice are mild and resolve spontaneously (Srgo 2006). However, in rare cases babies can have very high levels of bilirubin that can lead to bilirubin encephalopathy and kernicterus (Ebbesen 2005; Srgo 2006). The acute phase signs of kernicterus are poor feeding, lethargy, high-pitched cry, hypertonia or hypotonia, opisthotonos and seizures (Johnson 2002). The chronic manifestations include athetoid cerebral palsy, motor delay, gaze palsy, dental dysplasia, mental retardation and sensorineural hearing loss (AAP 2004). Studies from developed countries estimate the incidence of kernicterus to range from about 0.4 to 2 per 100,000 (Srgo 2006; Mannig 2007; Burke 2009). However, studies from developing countries suggest that the incidence may be much higher (Nair 2003; Owa 2009). Following guidelines issued by the American Academy of Pediatrics for the management of jaundice in the neonate (AAP 2004), the age-long critical cut-off value of total serum bilirubin (TsB) of 20 mg/dL (342 µmol/L) at which therapy was required is being replaced by a plot of TsB against time (hours) for each baby. This is compared to the nomogram for the age of the baby and used to determine the line of management (Higgins 2012). Current treatments for hyperbilirubinaemia include phototherapy and exchange transfusion, which is usually used for severe cases of hyperbilirubinaemia (Woodgate 2015).

Index test(s)

Transcutaneous bilirubin (TcB) measurement is a non-invasive method for measuring serum bilirubin level (Dai 1997). Transcutaneous bilirubinometry works by directing light into the skin and measuring the intensity of the wavelength of light that is returned (Boo 2007). Transcutaneous bilirubinometry is based on optical spectroscopy, which relates the amount of light absorption by bilirubin to the concentration of bilirubin in the skin. The technology was first introduced in 1980 (Yamanouchi 1980). The measurement is usually taken by gently pressing the meter against the sternum or forehead. Transcutaneous bilirubin measurement provides an immediate (less than a minute) result of bilirubin levels (Dai 1997). Using this point-of-care device saves time compared to measuring serum bilirubin and may reduce costs associated with measuring serum bilirubin in newborns (Maisels 1997). However, the accuracy of TcB results may be affected by gestational age, body weight and skin colour (Knüpfer 2001; Karen 2009). For example, TcB tends to underestimate TSB in light and medium skin colours and overestimates in dark skin colour (Samiee-Zafarghandy 2014). There are a number of TcB devices available, including the Bilicheck device, JM 103 and JM 105 devices (Grohmann 2006).

Clinical pathway

Newborns are routinely monitored by nursing staff and physicians for the development of jaundice in the first few hours of life and before discharge from the newborn nursery. This is usually done by visual inspection and skin blanching to assess for yellowish discolouration. Visual estimation of bilirubin level is not reliable (Barrington 2012). Therefore, bilirubin level needs to be assessed objectively by means of a TcB or TsB measurement. In some settings, TcB or TsB measurements are performed on all newborns as part of routine screening before hospital discharge or as targeted screening based on risk factors for severe hyperbilirubinaemia. Some of the risk factors include breastfeeding, ABO/Rhesus incompatibility, glucose-6-phosphate dehydrogenase deficiency, use of oxytocin during delivery, vacuum-assisted delivery, prematurity, and history of jaundice in a sibling (AAP 2004; Keren 2005; Bhutani 2010). TcB or TsB measurement can be done as part of universal screening or only if a newborn is visibly jaundiced and the value is plotted on a nomogram to assess the need for treatment (AAP 2004). In addition, the measurements may be taken on newborns undergoing phototherapy to help in making a decision on when to stop treatment. The bilirubin levels are interpreted based on the infant's gestational age and postnatal age (AAP 2004).

Role of index test(s)

The TcB assay is a non-invasive method for measuring bilirubin levels and it may help to reduce the risk of anaemia and trauma associated with blood sampling for TsB measurement (Dai 1997). TcB has been shown to work well in both hospital and outpatient settings; and has been shown to be better than visual inspection for estimation of hyperbilirubinemia (De Luca 2008; Wainer 2012). Additionally, the TcB measurement ensures a readily available result for immediate clinical decision-making while reducing the chances of infections associated with all invasive procedures (Jangaard 2006). The TcB meter can be used as a screening tool to estimate the serum bilirubin level in newborns who are not clinically jaundiced or as a diagnostic tool in jaundiced newborns to assess the need for treatment (AAP 2004).

Alternative test(s)

Various methods are used to determine bilirubin levels in newborns. These include visual assessment, direct spectrophotometric methods (requiring capillary blood) and use of an icterometer (Higgins 2012). Visual assessments for jaundice are common in newborn nurseries and outpatient settings, such as physicians' offices (Harrison 1989). However, studies have shown that the severity of jaundice cannot be assessed through visual estimation. The icterometer is a specialized ruler marked with different shades of yellow used to estimate the bilirubin level when pressed against a newborn's skin (Akman 2000).

Rationale

Bilirubin measurement is one of the most frequently performed tests in newborn infants (Donzelli 2000; Madsen 2000). Chemical methods for serum bilirubin measurement is currently the reference standard for measuring bilirubin levels. However, this requires repeated blood sampling which can be painful to the newborn, costly and time consuming. Transcutaneous bilirubin measurement has been recommended as a more cost-effective and less traumatic method of measuring bilirubin levels in newborns (Dai 1996). In order to justify routine use of TcB devices, we need to systematically review all the available evidence from well-designed studies on the accuracy of TcB measurements in newborn infants. A clear understanding of the diagnostic test accuracy of transcutaneous bilirubinometry using a variety of instruments in a variety of populations (including preterm and term infants as well as infants with various racial backgrounds) would be invaluable for understanding the usefulness of TcB measurement in newborns.

OBJECTIVES

- To determine the diagnostic accuracy of TcB as:

i) a diagnostic test for hyperbilirubinaemia in newborns suspected to have hyperbilirubinaemia on visual inspection;

ii) a diagnostic test for monitoring bilirubin levels in newborns receiving treatment (e.g. phototherapy) for hyperbilirubinaemia.

- To determine whether the gestational age, postnatal age, body weight, race and site of TcB measurement have any influence on the accuracy of TcB measurement for hyperbilirubinaemia in newborns.

METHODS

Criteria for considering studies for this review

Types of studies

We will include diagnostic test accuracy studies comparing TcB and TsB measurement for hyperbilirubinaemia in newborns, as follows.

- Cross-sectional studies.
- Cohort studies.

We will exclude all randomised controlled trials, retrospective studies, case-control studies, case reports and any studies in which data for true positives, true negatives, false positives and false negatives cannot be determined. Retrospective studies will also be excluded.

Participants

We will include studies evaluating infants aged 0 to 29 days (including term or preterm newborns) who require bilirubin measurement either as a universal screening test or a test for visible jaundice or for monitoring therapy for hyperbilirubinaemia. We will include studies conducted in different patient settings such as neonatal intensive care units, paediatric emergency units, paediatric wards and studies that recruited participants from home or in the communities.

Index tests

We will include studies that assessed the accuracy of any TcB device in newborns.

Target conditions

The target condition is hyperbilirubinaemia requiring treatment either by phototherapy or by exchange transfusion.

Reference standards

The reference standard is TsB measured in the laboratory, which requires blood sampling from the newborn. TsB measurement can be performed in the laboratory using various methods such as high performance liquid chromatography (HPLC), Diazo-based methods, or other methods such as direct spectrophotometric methods (Kazmierczak 2002) and capillary electrophoresis (Higgins 2012). Total serum bilirubin measurement by the HPLC method is not subject to interference from haemoglobin or lipaemia. However, this method is costly, labour-intensive and not practical for routine use (Kazmierczak 2004). The Diazo-based methods are the most frequently used laboratory assays but may be affected by haemolysis (el-Beshbishi 2009). Total serum bilirubin measurement requires drawing of blood causing pain and trauma to the

neonate. Repeated blood sampling for TsB measurement can cause anaemia, especially in preterm neonates. Inter- and intralaboratory variability has been reported with measurements of TsB (Lo 2011).

Search methods for identification of studies

We will use the standard search strategy of the Cochrane Neonatal Review Group to identify all relevant studies without any language restriction. Methodological filters for diagnostic studies will not be used, to avoid missing out on some relevant studies. We will attempt to get translation for articles written in languages other than English. We will record any article for which we could not get a translation in the section 'Characteristics of studies awaiting classification'.

Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE Ovid (from 1966).
- Embase Ovid SP (from 1982).
- CINAHL (via EBSCOhost) (from 1982).

We will also search the following trial registries.

- ClinicalTrials.gov
- International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/)
- World Health Organization (WHO) International Clinical Trials Platform (ICTRP) Search portal (apps.who.int/trialsearch/).

There will be no date restrictions in the search of trial registries.
Our search strategy for Embase was developed by discussion between the author team and the Cochrane Neonatal Group's Trials Search Co-ordinator (Appendix 1). We will adapt it for use in other databases.
We will also conduct searches based on the Embase strategy to identify other potential studies in:

- DARE (Database of Abstracts of Reviews of Effects);
- MEDION database (for Systematic Reviews of Diagnostic Studies).

We will screen the reference lists of any relevant reviews from DARE and MEDION for potentially eligible studies.

Searching other resources

We will examine the references lists of all included studies for possible additional studies.

Data collection and analysis

Selection of studies

Two review authors will independently assess eligible articles for inclusion from the titles and abstracts obtained in the initial search. They will resolve any disagreement through discussion or, if necessary, by involving a third review author.

Data extraction and management

Two review authors will independently extract data on study characteristics using a standard data extraction form. We will compute 2 × 2 tables of true positives, false positives, true negatives and false negatives, for the index tests at the thresholds reported. Where reported, we will exclude undetermined or indefinite results from the analyses. We will discuss differently extracted data until consensus is reached. The information we will extract from each study is presented in Table 1.

Assessment of methodological quality

Two of the authors will independently assess the methodological quality of each included study using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (Whiting 2011), which consists of four domains. We will develop a rating guideline for assessment of the domains in order to ensure consistency. We will assess each of the four domains with respect to the risk of bias. Additionally, we will assess the first three domains in terms of applicability. We will pilot our review-specific QUADAS-2 tool against five primary studies in order to identify possible areas of discrepancies between authors. We will make modifications to the tool if possible, to ensure consistency. We will resolve discrepancies in assessments between review authors by consensus. If this is impossible, we will seek final resolution using a third-party arbitrator. The items of the QUADAS-2 tool and our scoring interpretations for each item are presented in Appendix 2.

Statistical analysis and data synthesis

We will perform statistical analysis according to Cochrane guidelines for diagnostic test accuracy (DTA) reviews (Macaskill 2010). We will include studies reporting sufficient data that allows for the construction of a 2 × 2 table and also studies that only reported the Pearson correlation coefficients to describe the relationship between TcB and TsB measurements. The data from the 2 × 2 tables will be used to calculate sensitivity and specificity for each study and also meta-analysis of sensitivities and specificities where appropriate using the bivariate model if the same threshold for positivity was used. According to the bivariate method we will calculate overall sensitivity and specificity and their 95% confidence intervals (CIs), based on the binomial distributions of the true positives and true negatives (Reitsma 2005). However,

we anticipate that studies will use multiple thresholds, both between studies and within individual studies. If data with more than one positive threshold is reported within a study, we will extract the relevant data and present the findings graphically for each threshold. We will perform meta-analysis with the most common threshold where appropriate; and fit a summary receiver operating characteristic (ROC) curve using a bivariate random-effects model (Reitsma 2005). We will use the latest version of the Review Manager (RevMan) software to graphically present coupled forest plots, showing the pairs of sensitivity and specificity (and their 95% CIs) of each study, for each threshold. We will also present coupled forest plots of the Pearson correlation coefficients across studies where relevant, to allow basic visual inspection of individual studies only. All indefinite results will be excluded from the analysis.

Investigations of heterogeneity

The investigation of heterogeneity will be performed through visual examination of both the ROC plot of raw data and the forest plots of sensitivities and specificities. We will formally investigate potential sources of heterogeneity other than threshold effect in bivariate models if we have a sufficient number of studies. By fitting the covariates in a bivariate regression model, we will investigate the following sources of heterogeneity in the diagnostic performance across studies: type of TcB meter; gestational age (term versus preterm infants); race or skin colour; prior use of phototherapy; and reference standard. We will investigate the effect of these covariates by conducting subgroup analyses in the latest version of the RevMan software and by including each of these factors as covariates in the bivariate regression model. A minimum of 10 studies will be needed per covariate included in the regression model.

Sensitivity analyses

We will perform sensitivity analyses on the different domains scored on the QUADAS-2 tool, in order to explore the influence of the quality of the included studies. We will perform additional sensitivity analyses if other suitable factors are identified during the review process and any such analysis will be reported as 'post hoc' in the final review.

Assessment of reporting bias

We are not planning to use funnel plots to evaluate the impact of publication bias or other biases associated with small studies.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Data from each study

[Study ID]	First author, year of publication
Type of study	Journal article, unpublished data
Participants	Sample size Country of study Baseline characteristics (gestational age, postnatal age, race, body weight)
Study design	Retrospective/prospective design Sample (consecutive, random or unclear)
Study criteria	Inclusion criteria Exclusion criteria
Reference standard	Name of assay/manufacturer Name of instrument Cut-off values Time between reference standard performance and TcB measurement Blinding of operator to TcB result
Index test	Name of device Cut-off values Operator training site of measurement (forehead, sternum)
Target condition	Universal screening of newborns for hyperbilirubinaemia Diagnostic determination of hyperbilirubinaemia in visibly jaundiced newborns Monitoring of bilirubin in newborns on therapy for hyperbilirubinaemia

Table 1. Data from each study (*Continued*)

Data	Number of true positives and false positives Number of true negatives and false negatives Number of undetermined/uninterpretable results Sensitivity and specificity of index test Number of missing results for index test Number of missing results for reference standard
Notes	Source of funding (whether any author is affiliated with the manufacturer of the index test; the study was directly funded by the manufacturer; authors reported conflicts of interests related to the manufacturer or other funding sources)

APPENDICES

Appendix 1. Embase search strategy

Our search strategy for Embase OVID below was developed by discussion between the author team and the Cochrane Neonatal Group's Trials Search Co-ordinator. We will adapt it for use in other databases.
(infant, newborn or neonat* or premature or very low birth weight or low birth weight or VLBW or LBW or infan*) AND ((transcutaneous adj2 bilirubin) OR TcB OR bilicheck OR bilichek OR JM-103 OR JM-105 OR bilirubinomet* AND ((blood* or serum) adj bilirubin) OR TsB OR spectrophotomet*).mp

Appendix 2. QUADAS-2 tool

QUADAS-2 tool: Risk of bias and applicability judgements

Domain 1: Patient selection	**Domain 1: Pati**
A. Risk of bias	
1. **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear "Yes" if it is clearly stated in the paper that a consecutive or a random sample of patients was enrolled "No" if the patients were not recruited consecutively or the sample was not random "Unclear" if there is insufficient information to answer "yes" or "no"

(*Continued*)

2. **Was a case-control design avoided?**	Yes/No/Unclear The answer will always be "yes" since the review will exclude case-control studies
3. **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear "Yes" if the stated inclusion and exclusion criteria are clear and appropriate "No" if the stated inclusion and exclusion criteria include inappropriate subjects "Unclear" if insufficient information is available to answer "yes" or "no"
4.**Could the selection of patients have introduced bias?**	RISK: Yes/No/Unclear "No" if questions 1 and 3 are answered "yes" (Low risk). "Yes" if questions 1 or 3 is answered "no" (High risk). "Unclear" if insufficient information is available to answer questions 1 or 3
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	**Describe includ use of index tes**
1. Is there concern that the included patients do not match the review question?	CONCERN: Yes/No/Unclear "No" when the study population represents an unselected sample of newborns expected to receive TcB assessment for hyperbilirubinaemia (Low) "Yes" if included patients are inherently different from those expected to receive TcB assessment for hyperbilirubinaemia (High) "Unclear" if there is insufficient information to make a judgement on the patient inclusion (Unclear)
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	**Domain 2: Ind *please complete***
A. Risk of bias	
Describe the index test and how it was conducted and interpreted:	**Describe the in preted:**
1.· **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear "Yes" if the paper states that the index test is interpreted by individual(s) who were unaware of the results of the reference test(s) "No" if the results of the index test were known by the individuals performing the reference test, or if the same individual performed both tests "Unclear" if there is insufficient information to answer "yes" or "no"

(*Continued*)

2. **If a threshold was used, was it pre-specified?**	Yes/No/Unclear "Yes" if a pre-specified positivity threshold was stated. "No" if a threshold was not pre-specified. "Unclear" if there is insufficient information to answer "yes"or "no"
3.**Could the conduct or interpretation of the index test have introduced bias?**	RISK: Low/High/Unclear "No" if questions 1 and 2 are answered"yes" (Low risk). "Yes" if questions 1 or 2 is answered "no" (High risk). "Unclear if there is insufficient information available to answer "yes" or "no" (Unclear risk)
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: Low/High/Unclear "No" if there are no concerns based on the information available (Low) "Yes" if the index test is not TcB measurement for hyperbilirubinaemia in newborns or if the conduct of the test or its interpretation is not applicable to the review question (High) "Unclear" if there is insufficient information to answer "yes" or "no"
Domain 3: Reference standard	**Domain 3: Refe**
A. Risk of bias	
Describe the reference standard and how it was conducted and interpreted:	**Describe the ref interpreted:**
1 **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear "Yes" if the reference standard is TsB measured by one of the laboratory methods mentioned in this protocol "No" if the above condition is not met. "Unclear" if there is insufficient information to answer "yes" or "no"
2 **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear "Yes" if it is stated that the individual performing/interpreting the results of the reference standard was kept unaware of the results of the index test "No" if the results of the TcB measurement were known to the individual performing/interpreting the reference standard "Unclear" if there is insufficient information to answer "yes" or "no"
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: Low/High/Unclear "No" if questions 1 and 2 are answered "yes" (Low risk). "Yes" if question 1 or 2 is answered "no" (High risk).

(*Continued*)

	"Unclear" if there is insufficient information to answer "yes" or "no"	
B. Concerns regarding applicability		
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: Low/High/Unclear "No" if the target condition is hyperbilirubinaemia in newborns (Low) "Yes" if the target condition is not hyperbilirubinaemia in newborns or it is not clearly stated (High) "Unclear" if there is insufficient information available to answer "yes"or "no" (Unclear)	
Domain 4: Flow and timing		**Domain 4: Flow**
A. Risk of bias		
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): **Describe the time interval and any interventions between index test(s) and reference standard:**		**Describe any pa** **or reference sta** **(refer to flow di** **Describe the tim** **test(s) and refer**
1.· **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear "Yes" if the time between the index test and the reference standard is less than 30 minutes "No" if the time between the index test and the reference standard is longer than 30 minutes for a significant proportion of the patients "Unclear" if insufficient information is available to answer "yes" or "no"	
·2. **Did all patients receive a reference standard?**	Yes/No/Unclear "Yes" if all the patients who received the index test received a reference standard "No" if not all the patients who received the index test received a reference standard "Unclear" if there is insufficient information to answer "yes" or "no"	
·3. **Did patients receive the same reference standard?**	Yes/No/Unclear "Yes" if the same reference standard was used for all patients "No" if different reference standards were used. "Unclear" if there is insufficient information to answer "yes" or "no"	
4.· **Were all patients included in the analysis?**	Yes/No/Unclear "Yes"if all patients were included in the analysis,or if any withdrawals or exclusions are adequately explained with a flow chart "No" if withdrawals or exclusions are not explained or accounted	

(*Continued*)

	for. "Unclear" there is insufficient information to answer "yes" or "no"
Could the patient flow have introduced bias?	RISK: Low/High/Unclear "No" if questions 1, 2, 3 and 4 are answered "yes" (Low risk) "Yes" if any of the four questions is answered "no" (High risk) "Unclear" if there is insufficient information to answer "yes" or "no" (Unclear risk)

TcB: Transcutaneous bilirubin
TsB: Total serum bilirubin

CONTRIBUTIONS OF AUTHORS

Charles Okwundu conceptualised and wrote the draft protocol. Olalekan Uthman, Gautham Suresh, Johan Smith, Charles Wiysonge and Vinod Bhutani contributed to various sections of the protocol.

DECLARATIONS OF INTEREST

None known

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