PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of transcutaneous bilirubin measurement in managing neonatal jaundice in post natal ward of a tertiary care hospital in Pakistan
AUTHORS	Hussain, Ali Shabbir; Shah, Muhammad; Ali, Syed; Ariff, shabina; Lakhdir, Maryam; qaiser, fatima; Demas, Simon

VERSION 1 - REVIEW

REVIEWER	Chawla, Deepak Department of Pediatrics Government Medical College Hospital, Chandigarh, India Competing interests: None
REVIEW RETURNED	20-May-2017

GENERAL COMMENTS	In this manuscript, authors present the protocol of a study aiming to investigate the reduction in need and cost of blood sampling during management of neonates at risk of significant neonatal hyperbilirubinemia. There are many shortcomings in the protocol which need to be addressed. Abstract: The background is too long and methods to be used are too brief. Authors should specifically state the population being studied (neonates born in the hospital or those are admitted in any specific area of the hospital, their gestation and weight cut-offs), intervention being planned and outcomes being measured. Introduction is non-convincing and does not make the case for the study strongly. For example, it would be wrong to say that clinicians rely on clinically visible jaundice to diagnose hyperbilirubinemia. There is ample evidence and recommendations that clinical judgement is inaccurate especially in dark coloured neonates and TcB is preferred over visual assessment of degree of jaundice. There is no reference to the statement that only 27% clinicians are using TcB for assessing jaundice. Lastly it is not clear that authors are making the case for which of the following: accuracy of TcB vis a vis serum bilirubin, accuracy of TcB nomogram or ability of TcB to reduce blood sampling. Introduction needs to be written more specifically and with a better flow of ideas. Methods: It is not clear why authors want to exclude neonates at higher risk of hyperbilirubemia. It may be understandable to exclude preterm neonates, but why to exclude other neonates at risk; this will greatly reduce the number available. Further, authors have not mentioned the expected sample size. In the pre-intervention phase, how decision of taking serum sample will be taken is not clear. How Bhutani nomogram (which is for risk assessment) is combined with AAP nomogram of phototherapy thresholds is not clear?

	How safety of neonates post-intervention phase will be ensured is not clear? TcB may not perform well especially if bilirubin is above 13-14 mg/dL. Is there a fall-back to ensure that any neonate with significant jaundice is not missed because TcB is not able to pick up. Is not the monitoring of neonates for jaundice more intense (q 8 h) in the post-intervention phase? This may necessitate more samples than in the pre-intervention phase. For example if a neonate's level is between blue and red line as per protocol baby will keep on needing sampling every 8 till it goes above the red line or below the blue line. Secondary outcomes are not clear. Each TcB measurement is not clubbed with STB measurement and it seems that TcB will be measured only for a narrow range of STB. So how accuracy (by which I assume authors mean correlation and agreement, or is it diagnostic accuracy?) of TcB versus STB will be assessed. The cost of STB measurement should remain same in both phases of the study. What will be reduced is cost of care of a baby. So second secondary outcome needs to be revised. Lastly, many abbreviations of bilirubin have been used which is a bit confusing (e.g. TSBR vs TB and TcB vs,. TcBR). Recruitment is not a good word for use of JM 105 (page 4 line 46).

REVIEWER	Siddiqui, Naveed-ur-Rehman King Faisal Specialist Hospital & Research Centre Riyadh Saudi Arabia Competing interests: none
REVIEW RETURNED	27-May-2017

GENERAL COMMENTS	1)Study design not appropriately mentioned as pre and post analysis design is not enough, but not mentioned about whether it will be prospective or retrospective and if prospective will pre-implementation data will be taken retrospectively also not mentioned whether it will be observational cohort study etc. 2) nothing mentioned in the protocol about the consent process when and how it will be taken which is an important part of research ethics as it will involve a new intervention introduced during the study period 3) Author has not mentioned any thing related to sample size as mentioned in the introduction that previous study due to small sample size had shown insignificant results. therefore its very important to make sure the sample size should be appropriately calculated with alpha error 5% and beta error 10% to predict appropriate results especially when predicting a normogram for a given population which will require large sample size and also it needs to be adjusted with respect to all Pakistani full term neonates as the study population will only provide the normogram for that tertiary care hospital which will not be reflective of the whole population with in the country.

REVIEWER	Kuboi, Toru Department of Neonatology, Shikoku Medical Center for Children and Adults, Japan Competing interests: I declare no conflict of interests.
REVIEW RETURNED	29-May-2017

GENERAL COMMENTS	The authors reported the protocol of screening for neonatal hyperbilirubinemia using TcB nomogram. The authors made a practical protocol, and I could also sympathize. I hope that my comments are useful for the improvement of the article. My comments are as follows: 1. Is 'normogram' misspelling of nomogram? 2. What is the criteria of phototherapy in your institute? Bhutani's TSB nomogram? 3. I think that there is a problem with TcB nomogram how to create. 1) Bhutani's nomogram is based on White and African-American races. I suggest that you may investigate the natural course of TSB and TcB of your race. 2) In Pase 1, will not you miss cases who require phototherapy? I think it is desirable to obtain TcB and TSB in pair. Then, you will create your race original TcB nomogram. 3) The error between TcB and TSB is not always within ±1mg/dL. Because there are deviated cases, the setting including safer margin is required for TcB nomogram developing. 4. Reference number 13 is not appropriate.

VERSION 1 – AUTHOR RESPONSE

Reviewer's comments and our responses.

Reviewers comments:

Abstract: The background is too long and methods to be used are too brief. Authors should specifically state the population being studied (neonates born in the hospital or those are admitted in any specific area of the hospital, their gestation and weight cut-offs), intervention being planned and outcomes being measured.

Response:

Background reduced. Methodology elaborated and changes accommodated.

Please review in marked copy.

Reviewers comments:

Introduction: is non-convincing and does not make the case for the study strongly. For example, it would be wrong to say that clinicians rely on clinically visible jaundice to diagnose hyperbilirubinemia. There is ample evidence and recommendations that clinical judgement is inaccurate especially in dark coloured neonates and TcB is preferred over visual assessment of degree of jaundice.

There is no reference to the statement that only 27% clinicians are using TcB for assessing jaundice.

Lastly it is not clear that authors are making the case for which of the following: accuracy of TcBvis a vis serum bilirubin, accuracy of TcBnomogram or ability of TcB to reduce blood sampling.

Introduction needs to be written more specifically and with a better flow of ideas

Response:

Introduction modified to be more conclusive.

Reference given number 9.

Up till now we were exclusively using TSBR in our institute for assessment of neonatal jaundice. With the implementation of this quality initiative we aim to reduce the number of TSBR sampling by introducing TcBR nomogram.

Introduction completely rewritten

Reviewers comments:

Methods: It is not clear why authors want to exclude neonates at higher risk of hyperbilirubemia. It may be understandable to exclude preterm neonates, but why to exclude other neonates at risk; this will greatly reduce the number available.

Further, authors have not mentioned the expected sample size.

In the pre-intervention phase, how decision of taking serum sample will be taken is not clear.

How Bhutani nomogram (which is for risk assessment) is combined with AAP nomogram of phototherapy thresholds is not clear?

How safety of neonates post-intervention phase will be ensured is not clear? TcB may not perform well especially if bilirubin is above 13-14 mg/dL.

Is there a fall-back to ensure that any neonate with significant jaundice is not missed because TcB is not able to pick up.

Is not the monitoring of neonates for jaundice more intense (q 8 h) in the post-intervention phase? This may necessitate more samples than in the pre-intervention phase. For example if a neonate's level is between blue and red line as per protocol baby will keep on needing sampling every 8 till it goes above the red line or below the blue line.

Response:

Because a previous study done 25 years back from our institute did not show a good sensitivity and specificity with TcBR, we excluded all high risk babies. This will not affect the number of cases because in both groups (Pre and post implementation phase) same population (Low risk full term neonates) will be enrolled.

This is a quality improvement initiative therefore all babies who full fill study criteria will be enrolled during the study duration (6 months).

Data regarding Pre intervention phase will be collected from retrospective chart reviews/on line patient and laboratory data bases. Before implementation of this project all babies who appeared clinically icteric were subjected to TSBR sampling.(Please see pre implementation flow chart)

Thank you for pointing out. we aim to use AAP guidelines and have constructed our Nonogram by modifying AAP nomogram of phototherapy .please find changes in revised manuscript.

In pre implementation phase serum samples were sent for all those babies who appeared icteric on examination whereas In post implementation phase, all those babies who appear icteric will get a TcBR first and depending on the values of TcBR further action will be planned.(Please see the flow diagram figure 3). We have drawn blue line 2 mg/dl below phototherapy line to avoid missing any baby with significant jaundice.

To keep a safety net however we have allowed health care providers to send TSBR whenever they are not sure or feel that TcBR readings do not reflect their clinical judgment.

We have decided to monitor more frequently keeping safety factor in mind. Spacing it out might lead to delay in diagnosing significant hyperbilirubinemia. We also feel that frequent sampling will happen in in very few babies because it is unlikely that baby will continue to have TcBR level in between red and blue line as graph is ascending and TcBR will either go below blue line or will reach red line if increasing rapidly.

We believe that even then the total number of serum samples will be significantly lower than in pre Implementation group.

Reviewers comments:

Secondary outcomes are not clear. Each TcB measurement is not clubbed with STB measurement and it seems that TcB will be measured only for a narrow range of STB. So how accuracy (by which I assume authors mean correlation and agreement, or is it diagnostic accuracy?) of TcB versus STB

will be assessed. The cost of STB measurement should remain same in both phases of the study. What will be reduced is cost of care of a baby. So second secondary outcome needs to be revised.

Lastly, many abbreviations of bilirubin have been used which is a bit confusing (e.g. TSBR vs TB and TcBvs,.TcBR).Recruitment is not a good word for use of JM 105 (page 4 line 46).

Response:

We do not aim to establish the diagnostic accuracy of TcBR or its correlation with TSBR.

Our Prime objective is to improve the quality of care by reducing the number of serum sampling for neonatal hyper bilirubinemia using TcBR nomogram. However as a secondary analysis we will compare the TcBR result with TSBR results only for those babies whose TcBR and TSBR both are sent.

We feel that the number of TSBR will reduce significantly in Post implementation phase with the help of TcBR nomogram and therefore the cost of sampling will also reduce in this phase.

Thank you for the suggestions. Abbreviations reduced to TcBR and TSBR only. Changes amended in revised manuscript.

Reviewers comments:

1)Study design not appropriately mentioned as pre and post analysis design is not enough, but not mentioned about whether it will be prospective or retrospective and if prospective will pre-implementation data will be taken retrospectively

also not mentioned whether it will be observational cohort study etc.

Response:

Please find clarity in study design in revised manuscript.

Reviewers comments:

nothing mentioned in the protocol about the consent process when and how it will be taken which is an important part of research ethics as it will involve a new intervention introduced during the study period

Response:

This is a quality improvement initiative and therefore as an institutional policy we are not required to take consent from each and every patient. This study has been approved by the hospital's ethical review committee. (Ref #4742-Ped-ERC-2017) Document attached for reference.

Reviewers comments:

Author has not mentioned any thing related to sample size as mentioned in the introduction that previous study due to small sample size had shown insignificant results. therefore its very important to make sure the sample size should be appropriately calculated with alpha error 5% and beta error 10% to predict appropriate results especially when predicting a normogram for a given population which will require large sample size and also it needs to be adjusted with respect to all Pakistani full term neonates as the study population will only provide the normogram for that tertiary care hospital which will not be reflective of the whole population with in the country.

Response:

We aim to enroll all term, low risk neonates who develop clinical jaundice and who's TSBR or TcBR are done. As a quality improvement initiative we will have to enroll all babies within our inclusion criteria therefore cannot predict a sample size. We aim to enroll a large sample size as our nursery admits approximately 200-300 neonates per month which is way more than the previous study from our center 25 years ago which had a sample size of 65 babies.

We have constructed this nomogram to assist our health care providers to use the Transcutaneous bilirubinometer and send serum samples in a uniform manner and do not aim to validate the nomogram for the whole population.

Reviewers comments:

1. Is 'normogram' misspelling of nomogram?

Response:

Spelling corrected to nomogram

Reviewers comments:

What is the criteria of phototherapy in your institute? Bhutani's TSB nomogram?

Response:

We are currently following AAP guidelines for phototherapy threshold

Reviewers comments:

I think that there is a problem with TcBnomogram how to create.

1) Bhutani'snomogram is based on White and African-American races. I suggest that you may investigate the natural course of TSB and TcB of your race.

2) In Pase 1, will not you miss cases who require phototherapy? I think it is desirable to obtain TcB and TSB in pair. Then, you will create your race original TcBnomogram.

3) The error between TcB and TSB is not always within ±1mg/dL. Because there are deviated cases, the setting including safer margin is required for TcBnomogram developing.

Response:

We are using AAP guidelines effectively for many years and have not faced any problems with it.

In Phase 1, data will be retrospectively collected from chart review. All babies who fulfil the inclusion criteria will be enrolled.

We have constructed this nomogram to assist our health care providers to use the Transcutaneous bilirubinometer and send serum samples in a uniform manner and do not aim to validate the nomogram for the whole population.

We do not wish to establish the diagnostic accuracy of TcBR. It has been validated extensively and Dragger JM 105 is an FDA approved device for screening jaundice in neonate. Although the manufacturer states that the difference in reading can vary ±1mg/dL from TSBR we understand that there can be chances of errors especially at higher bilirubin levels and dark skin individuals. Keeping this in mind we have drawn the TcBR line at 2 mg/dl below the phototherapy line and have also kept a duration of 8 hour to recheck if the values of TcBR are between Red and blue lines. (Please review figure 2 and figure3)

Reviewers comments:

Reference number 13 is not appropriate.

Response:

Reference removed.

editors comments:

Change title to "Effectiveness of transcutaneous bilirubin measurement in managing jaundice on a postnatal ward in Pakistan".

Clarify if ethical approval has been obtained. Your study has commenced.

Response:

We have modified the title which is more reflective of the study design and outcomes.

Kindly review.

This study has been approved by the hospital's ethical review committee. (Ref #4742-Ped-ERC-2017)
Document attached for reference.