

09-17-8-2019

Dear eminent reviewers and editor:

Our group is obliged to express our thanks to our reviewers for their invaluable comments. By revising our manuscript according to reviewers' suggestions truly makes our study results more clinically relevant and scientifically sound. We also want to express our gratitude to the editorial office for giving us the opportunity to revise our manuscript. We will answer reviewers' comment point-to-point below.

Reviewer 03011144

Thanks for your insightful comments. You clearly point out some major problems we have faced for such a long time. Our recent change in national population policy obviously bring up this previously under-recognized problem.

-Was there any delay in recognition / diagnosis? (8/18 presented beyond 3 days)

As the regional referring hospital, all our patients were from other medical facilities around Hefei metropolitan area. The initial recognition of jaundice was made by all levels of medical professionals. The eight cases presented beyond three days were from rural area and most of their family had financial difficulty as reflected by some family refused blood exchange transfusion for that reason.

-Why did the study stop at 2 years, especially when the problem is uncommon?

Our group believe this is a medical problem previously not recognized due, at least in part, to the national one child policy. Although we only collected 18 cases over roughly two years the estimated number for our country, after the termination of the one child policy, will increase significantly. We agree it may be premature to share our results with our colleagues, but we also believe it is vital to call for our colleagues' attention for this surging medical problem.

-What are the primary and secondary outcomes of the study?

As a retrospective study our primary intention is to find out the prevalence of the previously ignored neonatal problem. We did introduce any intervention in this study so the primary and secondary outcomes were not described in the present manuscript.

-Has this study lead to a change in policy for screening for anti E in the children presenting with HDN?

We have just finished this study and attempted to establish our institutional guidelines for managing not ABO-incompatible HDN. The new implementations have been added in our revised manuscript. Most importantly, we have started to establish a research network for the whole Anhui Province to study this problem.

-Is there any correlation between Bilirubin levels and the age at diagnosis?

We did not see a correlation between the bilirubin level and age at diagnosis. The result has been added into our revised manuscript.

-What are the study limitations?

There are apparently several limitations in our study. As a medical facility of a developing country, we are not able to implement guidelines as effectively as well-developed countries. The lack of national guidelines for neonatal jaundice management and medical resource distribution are some major issue need to be resolved. This is also our major intention to share our findings relative premature so that we can improve medical service.

-What are the recommendations to prevent future anti E induced HDN?

We have added our recommendations in the discussion of our revised manuscript. As we expect the anti-E HDN will become more prevalent in the near future, a well organized research network is desperately in need.

Reviewer 03285323

I have read the manuscript entitled “Rh-incompatible hemolytic disease of the newborn in Hefei”. In this study, the authors explore the prevalence of hemolytic disease of the newborn (HDN) due to Rh-isoimmunization in their population. In general, this is a good designed study which would make positive contributions to pediatricians, neonatologists, obstetricians and transfusion experts practicing in this field. However, I have some drawbacks and suggestions which are: i) the authors could be use the statement of “non-Rh-D isoimmunization or “non-D Rh antibodies” instead of use of “minor blood group incompatibility” which also contain many blood groups mainly being as Kell; ii) written of the manuscript should be checked throughout the paper because some sentences were poorly expressed e.g. the sentence of “This incompatibility causes the mother’s immune system to generate IgG antibody against the blood type of the fetus” could be revised as “This incompatibility stimulate the mother’s immune system to generate IgG antibody against the blood type of the fetus which has been inherited from father”; the sentence of “The IgG antibody binds to fetal red blood cells transplacentally to cause hemolysis” could be revised as “The IgG antibodies across transplacentally and cause to hemolysis by bind to fetal red blood cells”; the statement of “mirror (Ballantyne) syndrome” could be corrected as “mirror syndrome (Ballantyne syndrome”); the sentence of the “Severe Rh-HDN can also lead to fetal demise, miscarriage, or premature birth” could be revised as “Severe Rh-HDN can also lead to miscarriage, fetal demise, or premature birth”; the sentence of “Blood types of parents and the newborns, hemolysis, and antibodies of minor blood groups were tested for ...” could be revised as “Blood types of parents and the newborns, parameters related to hemolysis, and non-D Rh antibodies were tested for ...”; “ the sentence of “... Rh-isoimmunization used to be the most common cause of kernicterus” could be revised “Rh-isoimmunization was the most common cause of kernicterus”; etc.; iii) there is a discordance between Abstract and text if 4,138 newborns admitted for neonatal hyperbilirubinemia had HDN?; iv) please further explain the Direct Coombs test, free antibody test, and antibody release test; iv) is the sentence of “During clinical work-up, caution needs to be paid for that direct Coombs test can be negative in severe Rh-HDN due to extremely high titer of the antibody” correct? Because this statement is valid for HDN due to ABO incompatibility and HDN due to Rh-incompatibility corresponding with positive Direct Coombs test, therefore please control that reference; v) letters and symbols used in the table are very small able to read, please give this table in a separate horizontal page.

Thanks for your suggestions to improve the readability of our manuscript. We have made all the corrections according to your suggestions. Unfortunately, we are not able to re-direct the orientation of the table in the word processor and the submission website will not accept two files for the original submission, so we are not able to make the amendment. However, we will try to submit the table as a supplementary file if the website allows us to do so for the resubmission.