Author’s response to reviews

Title: Initial and Delayed Thyroid-Stimulating Hormone Elevation in Extremely Low-Birth-Weight Infants

Authors:
Shin Ae Yoon (dalen@chungbuk.ac.kr)
Yun Sil Chang (cys.chang@samsung.com)
So Yoon Ahn (yoon.ahn.neo@gmail.com)
Se In Sung (sein.sung@samsung.com)
Won Soon Park (wspark6@gmail.com)

Version: 1 Date: 31 Jul 2019

Author’s response to reviews:

July, 31, 2019
Darren Byrne
Editor-in-Chief
BMC Pediatrics

Revision of BPED-D-18-00897

Dear Dr. Byrne:

Thank you for your kind consideration of our manuscript entitled “Initial and Delayed Thyroid Stimulating Hormone Elevation in Extremely Low Birth Weight Infants.” We would also like to thank the reviewers for the excellent and very helpful remarks. We have incorporated the comments, criticisms, and suggestions made by the editor and reviewers into our revised manuscript. Details are as follows:
Masahiko Kawai (Reviewer 1):

This is a retrospective evaluation of the clinical characteristics of ELBWIs with or without an elevation of TSH. Total number of the objects is relatively large, and some of the results are informative. However, there are several limitations although some of them have been already pointed out by authors themselves.

We are grateful for the reviewer’s kind comments on our revised manuscript. We have made some changes to improve the paper in strict accordance with the reviewer’s recommendation.

1. The reviewer stated “It is too long observational period. I wonder if some critical changes in therapeutic strategy could have affected the clinical parameters including thyroidal function tests. For example, use of iodine could affect the incidence of TSH elevation. At least, this limitation should be referred in the discussion.”

We are grateful for the reviewer’s insightful comments. We agree with the reviewer’s opinion that some critical changes in therapeutic strategy could have affected the clinical parameters, including thyroidal function tests. Indeed, we have observed that in parallel with the increased intact survival of ELBWIs due to better perinatal and neonatal intensive care, the incidence of THOP and subsequent TSH elevation was significantly reduced (Ref. 378). Although we have used 0.5% chlorhexidine instead of iodine as disinfectants for all the procedures at our institute throughout the study period, we have added in the Discussion section of the revised manuscript (Line 277-286, 332-334) that the lack of monitoring iodine exposure might be a limitation of this study.

2. The reviewer stated “The effectiveness of the supplementation of levothyroxine should not be discussed in this study. This is not a prospective study, and the medication is arbitrary. From this study, we cannot know whether levothyroxine could have affected the clinical courses. Considering these, Table 4, 5, 6 and the texts regarding with or without levothyroxine therapy should be omitted or summarized briefly.”

We are grateful for the reviewer’s helpful comments. Following the reviewer’s recommendation, we have deleted Table 4, 5, and 6, and summarized briefly that the levothyroxine medication was arbitrary, and therefore, we could not conclude whether levothyroxine affected the clinical courses, in our revised manuscript. We incorporated these changes into the Results (Line 224-233) and Discussion (Line 302-325) section of the revised manuscript. Please also refer to our response to comments #2 and 4 of Reviewer 2 (Dr. Paul B Kaplowitz).
Paul B. Kaplowitz (Reviewer 2):

Having recently reviewed the literature on this topic for a review article, I applaud the authors for their attempt to tackle a difficult and confusing topic and to come up with good explanations for their findings. Also the cutoff of < or >20 for normal TSH makes more sense than a cutoff of 5 or 1 or 15. Their literature review is all focused and reasonably complete. From this study, we cannot know whether levothyroxine could have affected the clinical courses.

We are grateful for the reviewer’s kind comments. We have made several alterations to improve our revised manuscript in strict accordance with the reviewer’s recommendation.

Specific comments:

1. It is important to include under methods the method for free T4 used during the study period and the normal ranges for different post-natal periods for term babies and premies if available. RIA methods are more like to give low results for sick premies than equilibrium dialysis methods and could explain why so many of their infants with delayed TSH rise had initially low FT4.

We thank the reviewer for the insightful comments. Following the reviewer’s recommendation, we have added details on the chemiluminescent competitive immunoassay method for free T4 used during the study period (Line 898-9189). We have used a universal normal range of 0.9–1.8 ng/dL for free T4 level regardless of postnatal periods in both term and preterm babies in this study.

Although we agree with the reviewer’s opinion that RIA methods are more likely to give low results for sick infants than equilibrium dialysis methods, our data showed a significant negative correlation between fT4 and TSH levels, a significant reduction of the incidence of THOP and subsequent TSH elevation along with an increased intact survival of ELBWIs. Moreover, the initial fT4 level was the best predictor for mortality and composite morbidities of ELBWIs, compared with the CRIB II and Apgar scores, as observed in our separate study (Ref. 387). Taken together, these data suggest that the severity of NTI rather than the
variation in fT4 measurement methods could explain why so many of our ELBWIs with delayed TSH rise had initially low FT4 levels. These views were incorporated into the Discussion section of the revised manuscript (Line 302-309).

2. In terms of measuring outcomes for treated and non-treated children, the fact that these 2 groups were not matched for severity of TSH elevation is important to emphasize and that makes it difficult to conclude that treatment with l-thyroxine was not beneficial though I suspect that is the case.

We are grateful for the reviewer’s thoughtful comments. Following the reviewer’s recommendation, we have emphasized that, as the groups for treatment and no treatment with levothyroxine were not matched for the severity of TSH elevation, it is difficult to conclude that treatment with levothyroxine was not beneficial. The new part is in the Discussion section (Line 302-325) of our revised manuscript.

3. The authors state that 95% of infants with delayed TSH rise were exposed to 1 or more stressors in the 2 weeks prior to the TSH elevation being detected. Can they state for comparison the % of controls without TSH rise who were subject to stressors during a similar time frame?

We are grateful for the reviewer’s sensible comments. We were unable to state for comparison the percentage of controls without TSH rise who were subject to stressors, as we could not set a specific date for comparison due to the wide time frame range when delayed TSH elevation was observed. However, considering the significant association of the extent of TSH elevation and fT4 reduction with the severity of stressors we observed in this study, we could assume that the percentage of controls without TSH rise who were subject to stressors might have been much less.

4. Under "Natural history and outcome of TSH elevation", it is stated that TSH elevation is always transient. That can clearly be stated for the ones who were never treated, but can it truly be said for the ones who were treated, TSH normalized as expected, and they remained on therapy for a mean of 625 days? Were the authors able to find the records of all these infants and see if they were eventually taken off treatment and what the results were? If so this would be very worthwhile information, as many clinicians are reluctant to discontinue treatment in children who at any time had a TSH of >100, feeling they likely represent "true" congenital hypothyroidism.
We are grateful for the reviewer’s helpful comments. In this study, all the infants showed a transient TSH elevation, and the infants with a TSH elevation even up to 667 remained normal up to 1 year after discontinuation of levothyroxine treatment. These findings suggest that all TSH elevations observed in ELBWIs mostly represent epiphenomenon of hypothyroidism due to NTI and are therefore transient in contrast to congenital hypothyroidism. We thus agree with the reviewer’s opinion that our data would reassure and encourage many clinicians who are reluctant to discontinue treatment in children that at any time had a TSH of >100, feeling they likely represent “true” congenital hypothyroidism, to discontinue medication. These views were incorporated into the Results (Line 215-6-222) and Discussion (Line 295-301) section of our revised manuscript.

5. Can the authors make some final recommendations as to the proper timing of TSH testing in ELBW infants and the proven transient nature of delayed TSH elevation for those whose highest TSH was <40?

We are grateful for the reviewer’s thoughtful comments. We recommend the establishment of a new routine regular follow-up TFT screening program at 4 week intervals or until the patient becomes clinically stable, especially in extremely preterm infants near the limit of viability who have the highest risk of developing delayed TSH elevation. For the infants with a proven transient nature of delayed TSH elevation and for those in whom the highest TSH was <40, TSH levels normalized at a mean age of 31 days. These views were incorporated into the Discussion section (Line 246-251, 295-301) (Ref. 24) of the revised manuscript.

We appreciate again the thoroughness with which the reviewers examined our paper, and we hope that it is now suitable for publication in the prestigious journal BMC Pediatrics. We look forward to hearing from you soon.

Sincerely yours,

Won Soon Park, M.D., Ph.D.
Department of Pediatrics, Samsung Medical Center
Sungkyunkwan University School of Medicine Seoul, Korea 135-710
Tel.: +82 2 3410 3523, Fax: +82 2 3410 0043
E-mail: ws123.park@samsung.com, wonspark@skku.edu