Author's response to reviews

Title: Risk of Cardio-Respiratory Dysfunction in Preterm Infants Placed in Car Seats: A Cross-Sectional Study

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To the Editor
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Re: Manuscript no 1281212125763714, entitled: Risk of Cardio-Respiratory Dysfunction in Preterm Infants in Car Seat: A Cross-Sectional Study

Dear Editor,

We are in receipt of your letter dated February 23 regarding the revision required to the above-mentioned manuscript and the enclosed comments from the experts in the field who evaluated the manuscript. Please thank the reviewers for their vigorous analysis and very valuable suggestions.

We have considered the points raised and respond as follows:

Response to the Reviewer Dr. Anne Greenough

Question 1. A convenience sample has been chosen; it is important to document what differences could be reliably documented in the sample size investigated and hence the readers can assess which negative results are due to type two errors.

Answer: Thank you for your comment. Yes, a convenience sample of preterm infants who were ready for discharge from NICU was used to test our hypothesis. The power for this study was calculated. Figure 1 represents the theoretical relationship between the power and sample size. An of Alpha <0.05 (two-sided) and a three-fold difference in the frequency of the occurrence of cardio-respiratory events during placement in the car seat (10% vs. 30%) was used to calculate the power of this study. The assumption regarding the frequency of cardio-respiratory events was based on previous the studies.1, 2, 3, 4, 5 The calculation revealed that a sample of 22 infant would be sufficient to maintain a power of 80%. Therefore, the 42 cases in our study show a power of 95%. The result of this power analysis is included in the manuscript (Material and Methods, sentence 5, 6, 7, 8).

Question 2. The repeatability of the outcome measures needs to be given, so again the reader can assess if the negative results are reliable.

Answer: Thanks for this question. We understand that repeatability is important for the identification of the significance of the results. To reduce random error and to increase the precision of the outcome measurements, a standardized (automated) technique for assessment cardio-respirator function in neonates was used (see “Study Procedures”). Additionally, the study procedure included serial measurements (by the same observer) on the same cohort of infants during the period of 45 minutes before placement in the car seat, 45 minutes during placement in car seat, and 45 minutes after reposition from the car seat. The automated technique and serial measurements are both important factors that improve the reliability of the outcome.
**Question 3.** The authors study the infants twice in the supine position, the results in the car seat should be compared to the average of the two supine position examinations to eliminate any bias as to timing of examination.

**Answer:** It is true that the measurements were conducted twice in the supine position. However, the pre-test position was not the same: before placement in the car seat (supine) as compared to after placement in the car seat (semi upright). We think that the combining of these two measurements will bias the results. Moreover, the cardio-respiratory events that were seen after repositions from the car seat to the supine position occurred in a lower proportion of infants and all of them had symptoms recorded prior to placement in the car seat. Therefore, combining the data will not increase the proportion of infants with cardio-respiratory events prior to the placement in the car seat.

**Question 4.** The authors do not introduce periodic breathings influence as an a priori hypothesis; this needs to be justified.

**Answer:** There are several reasons why the explanation regarding the periodic breathing was not stated in introduction: (i) the AAP did not include episodes of periodic breathing in the assessment of cardio-respiratory abnormalities during pre-discharge car seat testing of preterm infants; (ii) we did not specify the types of the cardio-respiratory dysfunctions in the hypothesis; and (iii) the description of periodic breathing is included in the “Methodology” section (see study procedure). Moreover, the importance of using periodic breathing for the assessment of preterm infants placed in the car seat has been discussed in the “Discussion” (see Discussion, sentences 21-23, 30-32). None of the previous studies had analyzed the risk of periodic breathing in conjunction with car-seat testing. Furthermore, the justification for the inclusion of periodic breathing in the assessment of cardio-respiratory function in neonates in the car seat has been provided (see Introduction, last two sentences).

**Question 5.** The results could be displayed in a more user friendly way less text and more tables.

**Answer:** In response to your suggestion, we created Table 1 to compare the prevalence of cardio-respiratory symptoms before, during, and after car seat testing (see Table 1 and changes in the Results). In addition, Figure 1 was created to explain the relationship between periodic breathing and other symptoms, and this reduces the text.

**Question 6.** There are a large number of comparisons it would be important to know this was taken into account when determining the limit of significance.

**Answer:** This study was designed to investigate the association between the position of the neonate (supine or semi-upright) and cardio-respiratory function (apnea, periodic breathing, bradycardia, and O2 desaturation). The data was analyzed to identify how gestational age at birth and weight at discharge influence on the cardio-respiratory function in neonates in different position (supine or up-right). Both exposure and outcomes were represented by the “yes” or “no” values in the measurements. Stratification was used to analyze the data separately in the supine and semi-upright position. Because of this design, we thought that the alteration of significance from the repeated measurements conducted twice in the same subject, i.e., before and after placement in the car seat, could be avoided. However, you are absolutely right in saying
that multiple comparisons have to be taken into account. Conditional regression analysis is one of the statistical methods that accounts for the impact of repeated measurements. Therefore, conditional regression analysis was performed to investigate the impact of conditions such as gestational age and weight at discharge on the development of a combination of cardio-respiratory symptoms in the neonates placed in the car seat in association with cardio-respiratory function in the supine position. The impact of gestational age and weight at discharge was not significant (Odd Ratio 5.4, 95% CI 0.42-69.2 and Odd Ratio 11.6, 95% CI 0.94-141.3, respectively). The results of the conditional regression analysis have been included in the manuscript (see Results, para 4).

**Question 7.** The patient population excludes all high risk cases who are most likely to have pre-existing cardio respiratory problems; the paper would have much interest if such infants were included.

**Answer:** The number of infants with such problems was very small. The vast majority of prematurely born infants were discharged from NICU in a stable condition. The only reason why we did not include high risk infants in this study is that an exacerbation of the symptoms is to be expected. Most of the infants with BPD and severe intraventricular hemorrhage are discharged from the hospital with O2 supplementation and on different medications. This limitation has been explained (see Discussion, last para).

**Question 8.** The authors acknowledge an important limitation of their study is they do not incorporate the duration of the cardiorespiratory event into their analysis.

**Answer.** Yes, we did acknowledge the limitation regarding the inability to incorporate the duration of cardio-respiratory event into the analysis. There were several reasons why we did not analyze the duration of the cardio-respiratory events. Firstly, the definition of apnea of prematurity and periodic breathing already includes the duration of the events. Secondly, the duration of bradycadia was <10 seconds in 95% of the tested infants and in 97.6% of infants during the placement in the car seat the duration of the decreased O2 Sat varied from 10 to 20 seconds.

**Question 9.** Were any of the infants taking medication for gastroesophageal reflux?

**Answer.** Thanks for your question. Infants included in the study were enrolled just prior to discharge from the hospital. As mentioned (in Material and Methods, sentences 8-9), none of the infants required oxygen supplementation or caffeine treatment for apnea of prematurity as well as medications for gastroesophageal reflux at the time of testing. We have dealt with the issue regarding medication for gastroesophageal reflux in the same sentence (see Material and Methods).
Figure 1. Association between sample size and power

References
Response to the Reviewer Dr. Alistair Gunn

Comment/Question 1. The only real limitation of the study is the short period of study. Several of the papers cited in this article, and others, make it clear that the infants sleep state is a major determinant of whether desaturation occurs (cf ref 16). From the methods, it is not clear what sleep state the infants were in during monitoring, however, the short interval suggests that they were mainly awake. During a longer period of transport, the infants would likely enter deep sleep and thus may be at higher risk of severe desaturations.

There is no mention of the possible role of recumbent car seats for transporting preterm infants or other possible approaches. In view of the present results, which confirm a very high rate of mild cardiorespiratory symptoms in all of their preterm infants, and some serious events in VLBW infants, even in short-term monitoring, should the authors consider recommending this approach at least for VLBW infants?

Answer: Thank you very much for these comments.

(1) How long should an infant sitting in a car seat be evaluated is still an open question. In this study, two approaches were used: the average time required for home-transportation of our patients and the methodological aspects that were used in other studies. Unfortunately, the majority of studies used 30 minutes and no more than an hour for testing the cardio-respiratory function in infants in the car seat. 1, 2, 3 Large controlled studies simply do not exist that could be used to justify a prolonged evaluation. Dr. Neil Stein in his Letter to the Editor 4 suggested that “only if the concern relates to the infant’s risk of central hypoxia or sudden infant death syndrome, then the infant should be evaluated differently.”

In our study, the total duration of the testing procedures was 135 minutes, which included three different stages: before placement in the car seat (45 minutes), during placement in the car seat (45 minutes), and after repositioning from the car seat (45 minutes). Moreover, during the 45 minutes of testing in the car seat, the majority of infants showed a high rate of mild cardio-respiratory symptoms.

(2) Your suggestion regarding the association between sleep state and the occurrence of cardio-respiratory dysfunctions is very important and we agree that it should be included in the discussion section (see Discussion). However, for the present study we did not record the stage and duration of sleep. Testing the influence of the sleep state on the occurrence of cardio-respiratory abnormalities in infants during their placement in the car seat is an excellent idea and it will be the subject of our next investigation.

(3) The approaches for the safe transportation of infants in order to reduce the occurrence of the cardio-respiratory dysfunction were tested in an excellent study by Tonkin and his colleagues 1 who found that a simple intervention reduced neck flexion and decreased the incidence of hypoxia. We have addressed the possibility of reducing cardio-respiratory dysfunction by using an alternative mode of transportation (see Discussion).
Comment 2. Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The authors need to:
1. Clarify the stage and duration of sleep during testing.
   Answer: During the 135 minutes of the car seat testing procedure (45 minutes before, 45 minutes during and 45 minutes after repositioning from the car seat) under the direct supervision of the investigator, all the infants were tested after they had been fed and settled, while they were quiet or sleeping, and left undisturbed during the testing procedure. However, the specific assessment of the sleep state was not conducted and it is admittedly a limitation in our study.

2. Insert adequate discussion of the important effect of sleep on risk of desaturations in a semi-reclining car seat, and the related potential limitations of the present study.
   Answer: The effect of sleep on the desaturations in the car seat and the related limitation in this study has been included in the Discussion (see Discussion).

3. On a related note, it is important to insert additional discussion of the potential danger of extrapolating from short-term monitoring to longer car trips, and the potential dangers for example of leaving babies asleep in a car seat. The authors clearly recognize this issue, but it is worth making it very clear.
   Answer: The correction has been made in the Discussion section (see Discussion).

4. Seriously consider whether in the final paragraph they wish to make a more general cautionary statement about whether VLBW infants should be transported supine?
   Answer: The corrections have been made in the Discussion section (see Discussion).

Comment 3. Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Methods, first line. What is a convenience sample? Is this meant to be “consecutive?”
   If so, the authors should provide the interval over which the infants were recruited.
   Answer: A convenience sample is a sample where the patients are selected, in part or in whole, at the convenience of the researcher. It is a non-probability sample. In this particular study participation was offered to all preterm neonates (gestational age ≤37 weeks) 24-48 hours prior to discharge from the Neonatal Intensive Care Unit (NICU) at St. Peter’s University Hospital between September 2002 to January 2003 except infants with major congenital anomalies, hypoxic ischemic encephalopathy, high grade intraventricular hemorrhage/ periventricular leukomalacia and severe bronchopulmonary dysplasia were eligible for inclusion in the study population.

Methods, second sentence. It is disappointing that so many infants who would be expected to be at higher risk were excluded. The authors should note this limitation in the discussion.
   Answer: The number of infants with such problems is very small. The vast majority of prematurely born infants were discharged from the NICU in a stable condition. There is
only one reason why we did not include high risk infant in this study: an exacerbation of the symptoms was expected. Most of the infants with BPD and severe intraventricular hemorrhage are discharged from the hospital with O2 supplementation and on different medications. The explanation regarding this limitation has been explained (see Discussion, last para).

Data analysis, first sentence. The analytical categories should be presented more clearly. eg. <28 vs. 28 to <37 weeks, <=2000 vs. >2000. This respondent urges the authors to use exactly the same labels as in the table and results.

Answer: The corrections have been made in the text and the Table.

2nd to Last sentence. Why is a date range given for the statistical software? It is more appropriate to state the version of the software.

Answer: The correction has been made (see Methodology under Statistical analysis).

last sentence. “percentiles”

Answer: The correction has been made.

Results Section

para 1, line 5. does this mean that ‘the few infants’ had repeated but mild symptoms? If so, this should be clarified.

Answer: Yes, it is correct. In the supine position (before placement in the car seat), mild symptoms were recorded in only 15/42 infants, whereas severe symptoms such as O2 Sat less than 80% and bradycardia less than 70 beats per minutes was not seen. The threshold for the identification of the severity of the events has been described (see “Methodology”, the last sentence under the “Study Procedures”).

para 3. this para needs to be reworded to present the findings more clearly, and to remove all the repetition of data from Table 1. This is not helpful, and as written overemphasizes non significant findings.

Answer: The changes have been made. The para 3 has been reworded (see under Results “As shown in Table 2...”). In response to the other reviewer’s suggestion, we added Table 1 to present the raw data. Therefore, Table 1 is now Table 2.

Figure 1 should be converted to Table 2, which is more appropriate for simple incidence data.

Answer: The data from Figure 1 has been incorporated into Table 2 (see Table 2)

Discussion Section

para 2 repeats a large section of results on periodic breathing even down to repeating the incidences and P value. This is repetitious and inappropriate. Results should be in the results only.

same para. The Yamamoto study demonstrated that peripheral desaturation caused severe cerebral desaturation. This should be stated more clearly.

Answer: The changes have been made. (see Discussion, para 2, reference 21).
The Yamamoto study was clarified by including additional information regarding the methodology that was used by the authors to investigate the cerebral desaturation. Actually, we started using and validated the same methodology in our NICU (for research purposes).

References