Author's response to reviews

Title: B-type natriuretic peptide and mortality in extremely low birth weight infants with pulmonary hypertension: a retrospective cohort analysis

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Author's response to reviews: see over
February 11, 2014

Journal Editorial Office
BioMed Central (Pediatrics)

RE: MS: 1434188675115693
B-type natriuretic peptide and mortality in extremely low birth weight infants with pulmonary hypertension: a retrospective cohort analysis
Alain Cuna, Jegen Kandasmy and Brian Sims

Dear Editor:

Thank you for your e-mail last January 16, 2014 regarding our manuscript (MS: 1434188675115693). We found the reviewers’ comments to be of great help in improving our manuscript. We are pleased to re-submit the following revised manuscript for your consideration. Please find in the following section our point-by-point response to the reviewers’ comments, as well as the changes made to the manuscript.

We believe these modifications have strengthened the manuscript. We appreciate your time in reviewing the revised version. Please do not hesitate to contact us for any questions for concerns. We look forward to your response.

Sincerely,

Brian Sims, MD PhD

Alain Cuna, MD

Jegen Kandasamy, MD
## Reviewers’ Comments and Authors’ Responses and Changes to the Manuscript

### Response to Reviewer’s report (Reviewer: Susan Ireland)

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<th>Reviewer’s comment</th>
<th>Authors response</th>
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<tr>
<td>#1 I have no recommendations for revision. The finding that a PDA may be significant in the long term survival of these babies is also interesting and may deserve further study in itself.</td>
<td>We would like to thank Dr. Ireland for her valuable opinions and her recommendations favoring publication of our study. We agree that the relationship between PDA and survival is interesting and needs to be investigated further.</td>
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### Response to Reviewer’s report (Reviewer: Kathryn Farrow)

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<th>Authors response</th>
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<td>#1 The authors report that in their population there is no difference in SGA status between the survivors and non-survivors. However, there is a significant body of data in the literature that SGA infants are at increased risk for BPD-associated pulmonary hypertension versus AGA infants (Bhat, et al. Pediatrics 2012; Check, et al. J Perinatol 2013). The present data would suggest that once these SGA infants develop the disease, they are at no greater risk to die than AGA infants. This is an important and novel concept that should be emphasized in the discussion.</td>
<td>We would like to thank Dr. Farrow for her careful and thorough review of our article. This is an excellent point. We agree with your insightful comment and have included a paragraph in the discussion highlighting this novel observation between SGA status and survival among infants with BPD-associated PH. Specifically, we stated the following: “More than one-third of infants with BPD-associated PH in our study were SGA. This is consistent with previous studies which reported that SGA infants are at an increased risk for developing PH.[5] [21] It is interesting to note however that no difference in SGA status between survivors and non-survivors was seen in our study. This may indicate that despite the higher risk for developing PH, SGA infants are not necessarily at any greater risk for mortality compared to appropriate for gestational age infants with PH. Larger prospective studies will need to be carried out to validate this hypothesis.”</td>
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The authors performed all of their analysis using the peak BNP levels, but as shown in Figure 1, there is a large amount of overlap between the levels in survivors vs. non-survivors. For those survivors with levels above the identified threshold of 220 pg/mL, did serial levels return to “normal” levels more quickly than the elevated levels in non-survivors? The authors themselves state that: “Serial BNP measurements may be helpful in identifying those infants at high and low risk for mortality.” It would seem from the methods that the authors already have some of this data from this population. Perhaps they could provide some insight in the discussion about trends, if the data are not yet statistically significant due to small sample size.

We thank the reviewer for this insightful comment and suggestion. We do have some data regarding serial BNP measurements, but the reviewer is correct in that our small sample size hampered our ability to perform statistically sound analysis of the data. Nevertheless, we followed your suggestion and looked at trends in our data. We did observe that survivors whose peak BNP levels were above the identified threshold of 220 pg/ml tend to have a decreasing trend over time to more “normal” levels (< 220 pg/ml). In addition, non-survivors tend to have persistently elevated levels (> 220 pg/ml) over time. We have included a paragraph discussing these observed trends, as indicated below. Thought not statistically significant, it is our hope that including these trends will help generate interest for larger prospective studies to answer more definitively the usefulness of serial BNP measurements as a prognostic biomarker in this population.

“Our analysis was limited due to the small sample size and the fact that BNP measurements were not obtained at similar time points. Nevertheless, we did observe trends showing that BNP levels decreasing over time were seen among infants that survived; and that BNP levels increasing or remaining elevated over time were seen among infants who died. This observation needs further validation in a larger prospective study with well-defined BNP estimation time points, but it does suggest that serial BNP measurement may be helpful in identifying infants at high and low risk for mortality; and that treatment, including the intensity of surveillance and the use of aggressive pharmacologic and interventional therapy, may be adjusted accordingly.”
In the discussion, the authors state, “An important limitation is the lack of follow-up data on survivors, including rehospitalization and post-discharge mortality.” However, in Figure 3, the authors present survival data for the patients with elevated BNP out to 600 days. Does that mean 20% of the patients with elevated BNP (approximately 3 patients) were in the hospital for almost 2 years before their initial discharge? Furthermore, Figure 3 would suggest that some late mortality for those with low BNP levels as the survival curve drops precipitously from 100% survival to 40% survival at 400 days. This is very confusing and needs clarification.

We confirm that some of the sickest infants in our study population have remained in our facility for approximately 2 years prior to initial discharge or transfer to another service (Pediatric ICU or Pulmonary). This is not uncommon as our unit is the only Level IV NICU in the whole state.

We appreciate the reviewer’s comment and are pleased to provide further details to clarify the drop in the survival curve observed in infants whose peak BNP levels were < 220 pg/ml. Upon review of our data, there were 4 patients whose peak BNP levels were below the identified threshold and yet did not survive. 2 of the 4 patients died from disease processes unrelated to PH (sepsis, withdrawal of support from global encephalopathy) which may explain why their BNP levels were not “elevated”. The remaining 2 infants did die from severe BPD and PH, yet their BNP levels were not “elevated” above the identified threshold. This may suggest that in a small number of infants with PH, BNP levels may not increase as expected. We have included the paragraph below in the discussion to further clarify this point.

“Four infants with peak BNP levels below the identified threshold of 220 pg/ml had late mortality, as reflected by a drop in their Kaplan-Meier survival curve at around 400 days of life. (Figure 3) Review of medical records indicate that the cause of death in 2 of these infants were due to disease processes not directly related to PH (sepsis, withdrawal of support for severe encephalopathy), which may explain why BNP levels remained below the threshold in these non-survivors. The remaining 2 infants however were identified to have died because of severe BPD and PH. This finding suggests that in a small subset of preterm infants, BNP levels may not rise as expected despite the presence of severe PH. Further studies...
are needed to validate this observation as well as identify characteristics that may determine which infants with PH fail to exhibit a rise in serum BNP.”

| #4 | There is a typographical error in the last sentence of the discussion. It should be “BNP levels will lead to decreased morbidity and mortality.” | We thank the reviewer for identifying this oversight. We have corrected this typographical error in the last sentence of the discussion which now reads as “BNP levels will lead to decreased morbidity and mortality.” |