Author's response to reviews

Title: Phenobarbital versus Morphine in the management of Neonatal Abstinence Syndrome, a randomized control trial

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Version: 4 Date: 27 September 2014

Author's response to reviews: see over
Dear Sir/Madam

Thank you most sincerely for your kind consideration of our paper entitled "Phenobarbital versus Morphine in the management of Neonatal Abstinence Syndrome, a randomized control trial" with the manuscript number of "MS: 9986270081386787".

Here I am submitting the answers to the comments of the reviewers and also the revised version of the paper that was changed according to the precious comments of the reviewers. We hope they are to your satisfaction and that of the reviewers.

Following, we provide the answers and changes made to the paper:

The primary concern of the reviewers was the chosen population, in several points I would like to address the reasons for choosing this population:

1. As the reviewer mentioned, the majority of the infants exposed to non-opioid drugs in utero, and many of the infants exposed to opioids in utero, do not need pharmacologic treatment, and non-pharmacologic approach is the first line of treatment, however a large percentage of the opioids exposed infants (Kraft WK, van den Anker JN. Pharmacologic management of the opioid neonatal abstinence syndrome. Pediatric clinics of North America. 2012;59:1147-65) and smaller percentage of non-opioid exposed infants require pharmacologic treatment. Including those who were only exposed to cocaine (Fulroth R, Phillips B, Durand DJ. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. Am J Dis Child. 1989;143(8):905–910) and those who were only exposed to methamphetamine (Smith L, Yonekura ML, Wallace T, Berman N, Kuo J, Berkowitz C. Effects of prenatal methamphetamine exposure on

2. Although non-pharmacologic treatment is the first approach to many of the infants with NAS, in this study the target population was only the infants who needed pharmacologic treatment. And many of the admitted infants with NAS who didn’t need pharmacologic treatment were not included in the study. This was mentioned in the manuscript in the lines 117 -119 in the inclusion criteria.

3. The majority of the available studies included the neonates who were born to opioid dependant mothers. As we mentioned in the manuscript in the lines 65 – 66, the prevalence of pregnant women who use illicit drugs other than opioids is growing and these drugs (cocaine, methamphetamine…) have also been described to cause NAS. Unfortunately research is lacking regarding the treatment of the neonates with NAS who require pharmacologic treatment who were born to non-opioid dependent mothers. In addition the previous studies that compared Phenobarbital versus Morphine in the treatment of NAS, only included infants who were born to opioid-dependant mothers. What is new in our study was involving the infants of mothers with substance abuse other than opioids and polysubstance users. This was mentioned in the manuscript in the lines 267-268 as one of the strengths of the study.

4. In many regions of the world the physicians face infants who exhibit NAS requiring pharmacologic treatment while they can not have an exact assessment of the drugs used by the mothers during pregnancy. Choosing the neonates born to mothers who used a variety of illicit drugs and a combination of the drugs in this study, could help in obtaining practical results for these physicians.

Major Compulsory Revision:
1. The duration of exposure is already mentioned in the "manuscript - results – descriptive statistics" section of the study; for the Morphine treatment group in the line 179 it is mentioned that "addiction duration was 4.4 ± 2.3 years" and for the Phenobarbital treatment group in the lines 183 - 184 it is mentioned that "maternal addiction duration was 3.8 ±3 years". The timing of exposure and other details was also mentioned in the manuscript in the "Method – study population and study design" section of the study. However in the lines 115 – 117, this statement was corrected as follows "exposure to addictive drugs in utero (determined by maternal history and confirmed by positive maternal urine toxicology screens during the last trimester of pregnancy)". All the mothers were using illicit drugs throughout pregnancy, but we couldn’t only rely on history, that’s why we included them based on positive urine toxicology results.

2. I do agree that opioid medications are recommended as first-line treatment for opiate exposed infants, but I disagree that Phenobarbital has fallen out of practice, especially for the neonates born to non opioids and poly substance dependent mothers. A very recent review by Kocherlakota that was published in the pediatrics 2014, stated that "Phenobarbital is a drug of choice for nonopiate NAS" and also it is stated that "phenobarbital is advantageous because it can be used as an adjuvant, especially in infants suffering withdrawal from polydrugabuse" also in the review of Grim et al., , clinics in perinatology, 2013, it was stated that "Phenobarbital tends to be more liberally used in neonates exposed to multiple substances" (Grim K, Harrison TE, Wilder RT. Management of neonatal abstinence syndrome from opioids. Clinics in perinatology. 2013;40:509-24).

3. A statement regarding the potential negative effect of using Phenobarbital in neonatal period was added to the manuscript in the discussion section ,lines 236 – 237 as
follows "However, concerns about Phenobarbital use in the literature include impairment of suckling, and adverse effects on the developing brain in long-term therapy"

4. In the Introduction section of the manuscript the lines 74 – 77, were changed as follows " Although non pharmacologic treatments have been proposed for the management of NAS, especially for the neonates born to cocaine or methamphetamines only dependent mothers,[5] most neonates with NAS require pharmacologic treatment.[4,9]"

5. The lines 68 – 71 and also the references were changed as follows " Among the neonates exposed to illicit drugs in utero, withdrawal signs and symptoms requiring medical intervention develop in 27-91%.[4] This rate is higher among poly substance and opioid dependent mothers and lower in stimulants only exposed neonates.[4,5,7]."

6. No multivariate model was used in analysis, because in the inclusion and exclusion criteria, most of the potential confounding factors were eliminated; IUGR, alcohol exposure, benzodiazepine exposure, breastfeeding, medical illness, neurologic abnormalities, were among these confounding factors. However one of the main limitations of our study was not excluding or measuring the nicotine exposure, this was mentioned as a limitation of the study in the lines 273 – 275 of the manuscript as follows "In this study women who used nicotine were not excluded of the study, since nicotine has been shown to affect the severity of NAS symptoms, this point should be considered when interpreting the results."

7. The exclusion criteria were chosen to minimize the factors that could bias the results of the study, most of the exclusion criteria has been shown to affect the severity of NAS, duration of therapy, or the requirement for treatment. These factors are also mentioned as the factors that could affect the severity of NAS in a very recent review
by Kocherlakota published in the pediatrics 2014 (Kocherlakota P. Neonatal abstinence syndrome. Pediatrics. 2014;134:e547-61). In addition alcohol use in pregnancy is extremely rare in our country, only one mother was using alcohol, and only two mothers used benzodiazepines.

8. In the limitations of the study the following sentence was added in the lines 275 – 276 as recommended "4. Due to the nature of the study, it was un-blinded; this could potentially affect as the results of the study."

9. Two references (numbers 4 and 5) were added to the manuscript. The other references of the manuscript were rearranged according to the added references.

**Minor Essential Revisions:**

1. The word "addicted" was changed to "dependent" through the manuscript as was recommended by the reviewer.

2. In the lines 91 – 92, "we couldn’t find" was changed to "no studies have compared".

3. The word "opiate" was changed to "opioid" through the manuscript.

4. The word "crack" was changed to "Cocaine" through the manuscript.

**Other changes:**

Dr. Hossein Dalili was assigned as the formal corresponding author of the paper, as stated in the title page.

Again I would like to thank you most sincerely for your precious comments; they were very helpful and helped us a lot in enhancing the quality of the paper.

Yours Sincerely

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