PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	STUDY PROTOCOL: TREATMENT WITH CAFFEINE OF THE VERY PRETERM INFANT IN THE DELIVERY ROOM: A FEASIBILITY STUDY
AUTHORS	Dani, Carlo; Cecchi, Alessandra; Remaschi, Giulia; Mercadante, Domenica; la Marca, Giancarlo; Boni, Luca; Mosca, Fabio

VERSION 1 – REVIEW

REVIEWER	Kamran Yusuf University of Calgary, Canada
REVIEW RETURNED	07-Jun-2020

GENERAL COMMENTS	This is feasibility study on a subject where research is sorely needed. I wish the authors success in this study so that they can pursue the clinical trial. Below are my comments. The study started in September 2019 and will continue till February 2021. Th number of participants so far, recruited is not mentioned. Their primary outcome are the levels of caffeine. Almost no center in North America and I suspect in Europe measures caffeine levels, give the wide range of the therapeutic levels. Can they give the rationale for caffeine levels as the primary outcome? How are they managing consents? Given that the infant has to be randomized within 10 minutes after birth and given the caffeine, are most of the consents antenatally? Even here women may be coming in labour or some indication for a C-section, not the best time to obtain consent. It is mentioned that randomization will be electronic. Can they provide more details about randomization? They have chosen caffeine to be given within 10 minutes after birth. Within these 10 minutes several things must be accomplished. Weight of the baby, delayed cord clamping, any possible resuscitation measures to mention a few. How frequently are they meeting their target? Would a slightly longer time limit have been better? If there is no blood sampling scheduled at the time of the second caffeine level, are the infants going to get a heel puncture just for caffeine levels? There is large amount of data being collected. The authors have not mentioned what is going to be done with this data. Can they provide a reference for the apneic spells criteria for intubation? Amongst the adverse effects, how will gastroesophageal reflux be assessed? In introduction, second line, probably a better word rather than crises can be found. Under study setting, please replace “third level” with “level three”.

	Under data collection, second line, gender should be replaced by sex, line 13" LPV "should replaced by" PVL". In line 17, by liquor culture, do the authors mean CSF?

REVIEWER	Charles C Roehr Newborn Care John Radcliffe Hospital Oxford University Hospitals Oxford UK
REVIEW RETURNED	15-Jul-2020

GENERAL COMMENTS	Interesting question, Hypothesis generating study. Very small n in total, making stratification by gestational age, etc. impossible Uncertainty of what level of Caffeine can be regarded therapeutic in preterm infants. Recent Caffeine review by Moschino L et al. 2019 (doi: 10.1183/23120541.00330-2019.) wold be worth including in the references.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1
Dear Colleague,
I would like to thank you for your comments. We found them very important and useful in completing and improving our study
Carlo Dani, MD

1.The study started in September 2019 and will continue till February 2021. The number of participants so far, recruited is not mentioned.
- To date, we have recruited 21 patients.

2.Their primary outcome are the levels of caffeine. Almost no center in North America and I suspect in Europe measures caffeine levels, give the wide range of the therapeutic levels. Can they give the rationale for caffeine levels as the primary outcome?
-We confirm that also in Italy caffeine level is not routinely measured. We decided to measure it to have objective evidence that caffeine administration has occurred successfully and that intravenous and enteral administration is equivalent or not. We reported this explanation in the revised text.

3.How are they managing consents? Given that the infant has to be randomized within 10 minutes after birth and given the caffeine, are most of the consents antenatally? Even here women may be coming in labour or some indication for a C-section, not the best time to obtain consent.
-You are right. As we explain in the revised text, "All consents will be obtained before the delivery, possibly at the time of admission of pregnant women at risk of preterm birth." We agree that it is not the best time to obtain the consent, but we think that we have not a better option.

4.It is mentioned that randomization will be electronic. Can they provide more details about randomization?
-We detailed that "The randomization sequence will be generated from the e-clintrials platform (https: // www. eclintrials.org/ect/O) whose manager is L.B.."

5. They have chosen caffeine to be given within 10 minutes after birth. Within these 10 minutes several things must be accomplished. Weight of the baby, delayed cord clamping, any possible resuscitation measures to mention a few. How frequently are they meeting their target? Would a slightly longer time limit have been better?
-We agree that 10 min are few. However, the need of mechanical ventilation due to the onset of relapsing episodes of apnea often occurs in the first minutes of life and, therefore, to have the best result from caffeine treatment it is opportune administer it as soon as possible. We are not sure that it is possible to give caffeine within 10 minutes after birth (although we are confident that it is), and this is the reason why we planned this feasibility study before to plan a further well-sized multicenter RCT to assess the effectiveness of caffeine treatment in the delivery room to decrease the need for MV in very preterm infants.

6. If there is no blood sampling scheduled at the time of the second caffeine level, are the infants going to get a heel puncture just for caffeine levels?
-As you know, the second dose of caffeine is commonly scheduled 24 hours after the first and, therefore, we believe that it is possible to perform simultaneous sampling for blood gas analyses (which are quite frequently needed in very preterm infants) and caffeine blood level measurements to avoid unjustified heel punctures.

7.There is large amount of data being collected. The authors have not mentioned what is going to be done with this data.
-Collected data will be used for detailing clinical characteristics of studied population. Moreover, we could compare clinical characteristics of infants who received enteral of intravenous caffeine. This will be important particularly if the two administration routes will be followed by different blood caffeine levels.

8. Can they provide a reference for the apneic spells criteria for intubation?
-Yes, we can, we added ref. #9 (Sandri et al., CURPAP Study, Pediatrics 2010)

9. Amongst the adverse effects, how will gastroesophageal reflux be assessed?
-We detailed that “Diagnosis of gastro-esophageal reflux will be made on the basis of clinical signs, such as persistent crying, irritability, back-arching, feeding, and frequent awakening 16.”.

10. In introduction, second line, probably a better word rather than crises can be found.
-We changed the term “crises” with “episodes”.

11. Under study setting, please replace “third level” with “level three”. Under data collection, second line, gender should be replaced by sex, line 13” LPV “should replaced by” PVL”. In line 17, by liquor culture, do the authors mean CSF?
-We made suggested corrections.

Response to Reviewer #2
Dear Colleague,
I would like to thank you for your comments. We found them very important and useful in completing and improving our study
Carlo Dani, MD

1.Making stratification by gestational age.
-Due to the relative small size of our population, we hope that it will be possible to stratify our results by gestational age.

2.Uncertainty of what level of Caffeine can be regarded therapeutic in preterm infants.
-We added a reference (#17, Moschino et al.) to support our definition of caffeine therapeutic level.

3.Recent Caffeine review by Moschino L et al. 2019 (doi: 10.1183/23120541.00330-2019.) would be worth including in the references.
-Please, see answer to previous point.

VERSION 2 – REVIEW

REVIEWER	Kamran Yusuf Department of Pediatrics, Cumming School of Medicine, University of Calgary, Canada
REVIEW RETURNED	11-Aug-2020

GENERAL COMMENTS	The authors have responded adequately to my comments. The revised manuscript should be accepted for publication.