Reviewer’s report

Title: The Minimally Effective Dose of Sucrose for Procedural Pain Relief in Neonates: A Randomized Controlled Trial

Version: 0 Date: 06 Jun 2017

Reviewer: Lynne Gerson Maxwell

Reviewer's report:

The authors (an impressive 17 individuals) report a rigorously designed and conducted randomized controlled study to determine the minimally effective dose of sucrose for procedural pain relief in neonates, having identified the use of a wide range of sucrose dose and concentration in previous studies of sucrose analgesia.

The fact that the study design utilized PIPP-R scoring of video recordings by unbiased coders with determination of inter-rater reliability in a small subset is admirable, rather than relying on real-time assessment.

The exclusion criteria cited include as noted on page 8, line 177-8, "unable to swallow, pharmacologically muscle relaxed) and or inability to assess pain accurately (e.g., the neonate's face was blocked with ventilator taping). Is it correct and wouldn't it be simpler to state that children who were intubated were excluded? (or is that an incorrect assumption on my part?). In the consort diagram, how many of the patients excluded for other reasons were excluded because of intubation or opioid administration?

The authors state that the adverse events resolved spontaneously without medical intervention (Page 15, line 285). Were there other interventions that the authors regarded as non-medical (e.g., back rubbing or other physical stimulation), especially for the children with oxygen saturation of <80% for > 20 seconds. This seems to be a dramatic event of some concern to have had absolutely no intervention. Was there really no oxygen, even blowby, administered to the neonates with this prolonged low saturation? Did the protocol include any recommended interventions for low saturation?

Discussion:

The authors state "we found higher pain scores were associated with younger and more preterm neonates (page 16, line 313). Was the magnitude of the difference possibly related to the fact that younger GA in itself causes the score to be higher? Or was the magnitude of the difference greater than what was added due to GA? The information in Table 3 makes it difficult to
understand the magnitude of the difference between GA groups, where only Spearman's correlation and p values are given but not the actual PIPP-R scores by GA.

Since some prior studies used an even lower dose of sucrose (0.05ml) do the authors think there is any reason to suspect that this lower dose might also be effective and should be assessed in future studies? The authors should give some rationale for why this study needed to be done (other than the reported adverse events, is there any downside to giving 0.5 or 1 ml sucrose rather than 0.1 ml?).

Specific editorial comments:

Page 16, line 297: Change "Exposure to a very small dose of sucrose" to "Oral administration of a very small dose of sucrose"

Page 19, line 376: change "terms" to "term"

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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