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Reviewer comments:

1. Clarify the frequency of the maintenance dose for caffeine (10mg/kg/? caffeine base) (para 2, Section on Caffeine vs theophylline / dosage)

The frequency of maintenance dose for caffeine is now displayed page 6, para 2) as advised.

2. Clarify the comparator for the NNT : 3 in infants less than 28 weeks and treated with high dose therapy (para 1, Section on Prevention of extubation failure)

The comparator for NNT is already mentioned in the same paragraph in a previous sentence " number needed to treat (NNT): 7" please see page 11, para 1).

3. Consider using "adverse effects" instead of "side effects" for clarity (see conclusion and table 1)

"Side effects" were changed to "adverse effects " as advised.

4. Methylxanthines can increase the secretion of gastrin (para 1, Section on Gastrointestinal) Feurle G, Arnold R, Helmst?dter V, Creutzfeldt W. The effect of intravenous theophylline ethylenediamine on serum gastrin concentration in control subjects and patients with duodenal ulcers and Zollinger-Ellison syndrome. Digestion. 1976;14(3):227-31. (PMID: 955329)

We have added this important information to page 17, section on Gastrointestinal) and consequently we added reference # 139 to the reference list and the rearranged the references accordingly.

5. In the conclusion, clarify the "therapeutic window" under the section on Dosage in the manuscript

The first sentence in the conclusion (page 19) is now rephrased to "Caffeine is the preferred first-line of treatment of AOP as it has a wider therapeutic range and is associated with less adverse events compared to theophylline".

6. In the conclusion, state "efficacy of caffeine therapy" instead of "value of caffeine therapy" for infants older than 34 wks gestation

"Value of caffeine therapy" was changed to "efficacy of caffeine therapy" in the conclusion page 20 as advised.

7. Table 1. Clarify the frequency of the maintenance dose for caffeine and theophylline

We thank the reviewer for this comment, the frequency of the maintenance dose for caffeine and theophylline is now displayed in table 1.

8. Use dysrhythmia instead of arrhythmia under adverse effects for caffeine and theophylline

the word "Arrhythmia" was replaced by "dysrhythmia" in table 1 as advised.

9. Under metabolism, clarify the difference between caffeine and theophylline in neonates. For example, caffeine and theophylline undergo N-demethylation via CYP1A2, but theophylline undergoes 8-hydroxylation via CYP1A2 and CYP2E1

We thank the reviewer for this comment, the differences in metabolism between caffeine and theophylline were added in table 1, metabolism section.

10. Would place "elimination" beneath "inter-conversion" and delete excreted unchanged under metabolism

Suggested changes were done in table 1

11. Provide a reference for the reported clearances for caffeine and theophylline

We apologize for the typo error in table 1 for values of clearance rates for caffeine and theophylline which changed to 0.002 to 0.017 (L/kg per hour) for caffeine and 0.02 to 0.05 (L/kg per hour) for theophylline accordingly we added references # 9,43.

12. Table 2. Use the past tense in the column for “main results” and consider including the country of the study for the various trials

The required changes in table 2 were done as advised.