Author's response to reviews

Title: How effective is Ametop 4% gel, before a peripherally inserted central catheter, in reducing procedural pain in infants: a randomized double-blind placebo controlled trial [ISRCTN75884221]

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Author's response to reviews: see over
To: BMC Pediatrics Editorial Board

Ottawa, February 6th, 2006

RE: revision of our manuscript `` How effective is Amethocaine 4% gel, before a peripherally inserted central catheter, in reducing procedural pain in infants: a randomized double-blind placebo controlled trial [ISRCTN75884221]

We would like to thank the reviewers for their constructive comments and suggestions. All the reviewers`comments have been addressed. Find below a point-by-point description of the revisions made or answers to reviewers`questions. A revised manuscript has been submitted.

Major compulsory revisions:

Reviewer 1

As suggested, the generic drug name, tetracaine, is now used throughout the manuscript.

1. An abstract has been added to the manuscript. It had previously been uploaded onto the submission form, but not in the body of the manuscript. This has been rectified.

2. More information on rationale for the study is needed in light of previous similar study previously published.

When our study was planned, Ballantyne`s study was ongoing, with recruitment about a third of the way. Since then, Ballantyne et al have completed their study and published results in December 2003. They were the very first ones to publish a study using tetracaine in premature infants for PICC line insertion. Their total sample size was 49 infants and infants 27 weeks or greater were included. As the infants most likely to need a PICC are those born at less than 28 weeks of gestation and, as the total number of infants enrolled in trials was small, we felt another trial was justified. We included infants as small as 24 weeks gestation, being the first ones (to our knowledge) to recruit such small infants in a clinical trial involving tetracaine. As equally novel, we monitored “biochemical safety parameters” ie creatinine, transaminases, platelet, hemoglobin and neutrophils values, as little is known about possible side effects of tetracaine in premature infants.
Two sentences have been added to complement the rationale, on page 5, 2nd and 3rd paragraph.

3. Indicate who obtained consent.

Consent was obtained by a research team member (DH) or our research assistant, at arms-length of clinical care.

This was added on page 7, 2nd paragraph.

4. Specify the drug was administered under occlusion and specify the dose

The drug has indeed been administered under occlusion (sterile Saran Wrap). This was chosen rather than a sticky occlusive dressing, to prevent skin injury on removal). A sentence was added, page 7, 3rd paragraph.

We used tubes of 1.5g of tetracaine. Our pharmacist, to preserve the double blinding, extracted the drug from the tubes and placed it in ointment jars. The mean weight of drug that she could extract was 1.1g. This was specified better in paragraph 3, page 7.

5. What was the stability of the drug, when removed from the original package?

The manufacturer specifies the drug can be stored at room temperature for up to a month, but does not have specific recommendations once package has been opened. Our research pharmacist had conversations with the manufacturer (personal communication, Jason Collins, Smith-Nephew, Ville St-Laurent, Quebec, October 2001), who suggested placing the drug in small ointment jars, as if the tetracaine was stored in a tightly sealed container avoiding evaporation, this would prevent crystallization. He recommended a maximum period of 28 days before discarding unused doses of gel. After opening the original package, the drug was kept in the climate controlled unit medication refrigerator for up to 28 days. If not used by then, it was discarded and another dose was prepared. The mean time elapsed between preparation of the study drug and its use was 16 days. We did not observe or feel any crystallization of the drug during the study. Perhaps the refrigeration slowed the crystallization process down? It is not excluded that crystallization was missed in some cases, however, crystals or non-homogeneity should have been felt on application of the gel and our team members did not report that.

6. Delete paragraph 1, page 9

Since in fact, no infant received sucrose, this part of paragraph 1, page 9, has been removed as well as one sentence on page 14, paragraph 2.
7. Remove table 1 on page 9 and summarize info in manuscript

The table was removed and information summarized on page 9.

8. How was PIPP scored? Who recoded the tapes? Clarify intra-interrater reliability statistic used.

PIPP scores were assigned every minute during the PICC procedure, from baseline through to the recovery phase. Two specially trained facial coders assigned duration to the facial expressions (brow bulge, naso-labial furrow and eye squeeze), for each 30 seconds from baseline to recovery. After we had videotaped several procedures (enough to fill a tape), the tape was sent to Dr. Bonnie Stevens’ laboratory at The Hospital for Sick Children, Toronto, for the facial coders to code the facial expressions. One investigator (DH) calculated PIPP scores, using the raw data provided by the facial coders. Using the tool as it was originally validated, differences in oxygen saturation and heart rate were compared from baseline, to each minute after ‘poke’. Each PIPP score was derived by calculating two 30-second intervals for each minute of the procedure. The PIPP score was assigned as the highest value of the two 30 second scores. Prior to beginning the study, DH attended Dr. Stevens’ laboratory at HSC and thus was very familiar with the process for scoring PIPP.

The intra-interrater reliability stated on page 10, 4\textsuperscript{th} paragraph were measured at Dr. Stevens’ lab at the Hospital for Sick Children, using percent agreement. These tests were run on a regular basis during our study as well as other ongoing studies, to ensure reliability of the measurements.

This was clarified in the 1\textsuperscript{st} paragraph, page 11.

9. Clarify PIPP at first minute as primary or secondary outcome
   Is insertion phase same as skin puncture phase?
   Who measured ease of insertion?

The primary outcome was the PIPP at first minute. The secondary outcome was the independent and repeated PIPP scores, measured from the first to the fourth minute, analyzed with a Student’s t-test and a repeated measure analysis of variance, respectively. The methods section has been modified to clarify this point

The insertion phase begins at the skin puncture. The words (post-skin puncture) have been removed from page 11, 2\textsuperscript{nd} paragraph to increase clarity.
The ease of insertion was measured subjectively by the nurse inserting the PICC, according to how easy or difficult the procedure was, compared to her previous experience. We had speculated that, due to the vasodilatory effect of tetracaine, PICC insertions might be easier, as the vein may be easier to visualize. A sentence has been added on page 12, 1st paragraph.

10. Why were the blood tests specified used to assess safety? Was extra blood required for this purpose?

During the grant submission process and REB application process, we also had to apply to Health Canada to receive a letter of non-objection to our trial, since we were planning to use tetracaine off-label ie on infants less than a month old, which was the specified lower age limit by the manufacturer. In order to successfully obtain such a non-objection letter, we decided to include in our application this safeguard: we would look for “usual suspects” ie liver, kidney and marrow dysfunction, as possible side effects of this drug, since there was no data on safety in the premature population. Thus, ALT, AST, creatinine and CBC were added as parameters monitored. Most infants were on TPN and had regular checks of their ALT, AST and creatinine, thus did not represent an extra poke for bloodwork. In some cases it did mean obtaining a CBC earlier than clinically ordered and thus 0.3 to 0.5 cc of blood extra. This potential extra blood was well outlined in our consent form and approved by our REB.

A sentence was added paragraph 2, page 12.

11. On page 12, 2nd paragraph, cite Ballantyne’s trial

The reference was added in the 1st paragraph, page 13.

12. PIPP contains GA, so why is it adjusted?

This was an oversight. The sentence has been corrected, page 14, 1st paragraph and the repeated measure analysis was redone. Results remain unchanged (p=0.330 instead of 0.338). A sentence was added to clarify, page 15, 2nd paragraph.

13. The PIPP scores are lower for drug-this should be mentioned.

The PIPP scores are in fact slightly lower in the tetracaine group, 0.45 to 1.27 units lower than in the placebo group. A sentence has been added, page 15, 2nd paragraph.

Specify “mean oxygen saturation”, page 15, 1st paragraph.

That has been changed.
14. First paragraph of discussion weak-specify findings of the study.

A sentence has been added at the beginning of the discussion, stating our findings. The paragraph has been modified as well as the discussion itself, emphasizing possible reasons for the negative results.

15. Page 14, 3rd, paragraph: doesn’t appear to be relevant, delete.

This paragraph deals with the issue of dose of tetracaine and reasons why the drug may be ineffective or become ineffective. We feel this paragraph should be kept and we have added information on ineffectiveness. It can now be found on page 18, 2nd paragraph. The last part of the paragraph, which discusses duration of application, has been relocated to page 19, 1st paragraph.


The portion of the paragraph describing the post hoc analysis has been relocated to the results section, page 16, 1st paragraph. The discussion of why this analysis was done is detailed and discussed on page 18, 1st paragraph. We believe figure 2 adds value to this part of the discussion and would like to keep it as part of the manuscript.

17. Page 16, 3rd paragraph: sucrose not evaluated in this trial-may write about potential role. Why not discuss opioids also?

Infants in our trial did not meet eligibility criteria to receive sucrose, according to our unit protocol. We believe sucrose may have played a role in alleviating procedural pain. This is detailed on page 21, 2nd paragraph.

Discussion about the potential role of opioids can now be found on page 20, 4th paragraph and page 21, 1st paragraph...

18. Page 17, 2nd paragraph. Number of painful interventions likely to be balanced between groups. Don’t see this as a major limitation.

We did not see it as a major limitation either, but thought that, as a recognized confounder, it should be mentioned. A sentence has been added to that effect, page 20, 3rd paragraph.

Include information on why outcomes not available for all infants.

A sentence has been added, page 14, 3rd paragraph, to complement figure 1.
Discuss limitation of applying the drug for 30 minutes only. What was the elapsed time between drug removal and procedure?

Due to the extreme immaturity of a good proportion of our enrolled patients, an application time of 30 minutes was chosen, fearing too much absorption of drug via an immature skin. This is similar to Ballantyne. We waited 30 minutes before removing the drug. The mean time before removal of the drug and beginning of the insertion phase was 12 minutes. This limitation was acknowledged on page 19, 2\textsuperscript{nd} paragraph.

19. Page 17, 2\textsuperscript{nd} and 3\textsuperscript{rd} paragraph: conflicting information about using systemic analgesia vs sucrose. What do authors recommend? Why was study negative? Do they think local anesthesia offers any benefit at all?

The discussion about sucrose and systemic analgesia has been refined on page 20, 4\textsuperscript{th} paragraph and on page 21, 1\textsuperscript{st} and 2\textsuperscript{nd} paragraphs. We have discussed various points which can account for the negative findings: duration of application, limitations of the PIPP in extremely immature infants, possible ineffectiveness of the drug after a certain time out of the original package, sucrose not being used. The discussion has been revised. Given the available data from our study and Ballantyne’s, it appears that local anesthesia offers little benefit to reduce procedural pain due to a PICC insertion in immature infants.

20. Table 4: For number of attempts, is difference between 2 and 1 really 0?

The difference between the attempts is the difference between the median number of attempts. 0 is correct.

21. Figure 1: Can show number qualifying for secondary outcomes.

This figure is already quite detailed and follows the CONSORT statement. The number qualifying for each secondary outcome (except vital signs at each time point) is described in Table 3. We think it would be redundant to add that data/detail to figure 1.

Reviewer 2

1. An abstract must be added after the title page.

This has been added.

2. The PIPP was used in a modified way. Give reason, explain in detail how scoring was performed, advocate for the validity and reliability.
The PIPP was used according to the description by Stevens et al. We did not modify its use. Paragraph 1, page 11, details how the PIPP was used, to increase clarity.

3. Clarify in what way we believe our results are clinically significant, even if only a difference of 0.86 units on the PIPP scores were found between groups at 1 minute.

We agree that the difference found, 0.86 units is neither statistically significant, nor clinically significant, in the sense that it’s not really relevant clinically show that a drug decreases pain by 0.86 units. It doesn’t make a difference for the patient. The meaning of our statement, which has been clarified on page 16, 3rd paragraph, is that it is still relevant clinically, for those looking after similar infants, to know that tetracaine doesn’t significantly decrease pain.

**Minor essential revisions**

4. Correct the reference to the article by Simons et al: it is a prospective observational study rather than a RCT.

This has been corrected, page 4, 1st paragraph.

5. Median duration of crying in non-intubated infants is reported on page 12. I would like to know how many infants in each group were intubated during the observation.

That information can be found in Table 3: 15 infants were intubated in the placebo group (hence only 8 could have that outcome assessed) and 19 were intubated in the treatment group (hence 7 could have that outcome assessed).

6. Table 2 and Table 3: BW, GA and age in days should not be given with more than one decimal-figure.

That has been corrected on Table 1 and 2.

**Reviewer 3**

Authors should make more of a case about why they think their study adds something more than Ballantyne and in general.

We have added sentences on page 5, 2nd and 3rd paragraph to add to the justification to do our study. Basically, we recruited the smallest, most immature infants to our knowledge, in a study looking at tetracaine. These
are the infants regularly needing a PICC and data on safety and efficacy of tetracaine was needed. Our results add to the knowledge in that area. We also were the first to collect data on the biochemical safety of tetracaine in the neonatal population. This has been highlighted on page 18, 1st paragraph.

Discretionary revisions

Reviewer 2

Points 7, 8, 10, 11 and 13 have been addressed in the text.

Point 9: Reason to include heart rate and saturation as secondary outcomes when they are included in the PIPP.

The reason for including these variables was more as a monitor for extreme numbers, events, rather than aiming to compare them as “evidence” that pain was alleviated.

Point 14: We thought that clinically, a change of 3 in the PIPP was significant enough that we would consider implementing a change in practice. This was not based on pilot data, which, if we had to redo a similar study, we would get before starting, to better assess feasibility and sample size. The effect size of 2 is more a comparison, without justifying this would have been enough. A sentence was added on page 20, 2nd paragraph, to clarify.

Point 15: It is true that the discussion about sucrose won’t help answer the question whether tetracaine relieves PICC associated pain. However, interesting data suggests tetracaine or EMLA may not provide additional benefits in reducing pain when used with sucrose in venipunctures. Sucrose may be an alternative or an adjunct. Sentences have been added in the discussion and that point has been clarified.

Reviewer 3

It was clarified when we looked at younger babies separately in the last paragraph of the results section, page 16, 2nd paragraph.

Several of the infants were intubated with tape on their nose. Nasolabial furrow could thus not be assessed. Given that limitation, which comes with the population, analyzing the facial actions separately from the PIPP would likely not be useful, thus was not undertaken.