Reviewer’s report

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]

Version: 2 Date: 27 December 2005

Reviewer: Mats Eriksson

Reviewer’s report:

General

In general this is a well-written precise report of a well-conducted study. Procedures for patient enrolment, blinding/randomization, the power analysis and the statistical analysis are sufficiently described as well as the observed procedure and other comforting or pain-relieving methods being simultaneously performed.

The choice of pain assessment tools is appropriate. The PIPP score is widely used in modern neonatal pain research and its psychometric properties are well established. I do also find the parameters chosen for safety assessment being relevant.

The results are well described and the discussion covers the most important possibilities for the lack of group-difference in pain-reaction.

Below, I will give my comments on specific issues in the text. The page numbers refer to the pdf-copy of the manuscript I reviewed (http://www.biomedcentral.com/imedia/9527650958629149_article.pdf).

This is an interesting research report concerning a possible treatment in a neonatal age group where little research has been done on this specific topic. If the major questions can be sufficiently answered I highly recommend publishing.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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

2. The investigators have chosen to assess PIPP scores during the first, second, third and fourth minute (= 60 seconds) of the insertion phase (p. 8 – 9). The original PIPP-tool measures relative duration of three face expressions as well as increase (from baseline to maximum value) in heart rate and decrease (from baseline to minimum value) in oxygen saturation during the first 30 seconds following the observed procedure. I think the authors need to a) give their reason for this modified use of the PIPP-tool, b) explain more in detail how the scoring was performed (were changes in heart rate and saturation for the subsequent scorings compared to baseline before skin puncture or
to another time point?), and c) advocate for the validity and reliability of the PIPP instrument when used otherwise than described by the constructors (Stevens et al. Premature Infant Pain Profile: Development and Initial Validation. The Clinical Journal of Pain 1996;12:13-22).

3. The beginning of the discussion needs to be clarified. The authors were (correctly) conservative enough to hypothesize 3 units better or worse PIPP score in the Ametop than in the placebo group, though it could be assumed (hoped) that Ametop would lower the pain score. The results show a mean in the Ametop group that is 0.86 units higher (not significant). The authors state that despite this result they believe that their result is important clinically. I would like them to explain in what way (p. 13).

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

4. The article “Do we still hurt newborn babies?” by Simons et al. (reference 3) does not describe a RCT but a prospective observational study (p. 2).

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

6. Table 2 and Table 3 (p. 25). Birth weight, gestational age and age in days should not be given with more than one decimal-figure.

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Discretionary Revisions (which the author can choose to ignore)

7. As a result of remark 4, above under Minor Essential Revisions, RCT should be explained the first time it appears in the text, which now is in the second paragraph on p. 3: “Two RCTs reported…”

8. Reference 8, an article by Moore does not reveal whether the crying time was affected by the use of Amethocaine gel. In fact it does not give any pain score figures either, it just reports: “A Mann-Whitney U-test … returned a P-value of < 0.01…”. The statement in sentence three in the second paragraph on p. 3 should therefore be reformulated.

9. The secondary outcomes include heart rate and saturation (p. 9). These variables are also included in the PIPP instrument, which means a significant difference here would have been given double impact. Since no differences were found, this “double-scoring” is of less importance, but the authors might comment on their reason for including these variables twice.

10. On p. 9 it’s stated that vital signs and adverse events were recorded. For how long time after the procedure was this done?

11. The expression “similar populations” (second paragraph under Discussion, p. 13) is unclear. Similar to what? The studies mentioned earlier in the same sentence are all performed on older children.

12. The absence of a pain-relieving effect during heel-prick has also been observed for EMLA-cream. Larson and co-workers suggest that this might be an effect of variations in the local blood flow (Larsson et al. Regional variations in skin perfusion and skin thickness may contribute to varying efficacy of topical, local anaesthetics in neonates. Paediatr Anaesth 1996;6:107-110). The authors might want to discuss similarities with and differences from other EMLA-studies in neonates, for
instance on p. 13.

13. On p. 14 – 15 the authors suggest that inter-individual differences in response to medications could confound the results. This is true but in a correctly designed and conducted RCT such differences should be “randomized away”. The authors might consider rewriting this part.

14. In the second paragraph on p. 16 the authors discuss that an effect size of 2 PIPP units might have been a better aim in the power analysis. As we now know there was no difference, this is an unnecessary discussion. It would not have helped the study to reach statistical significance. The discussion ought to be about what is a clinically significant (or important – MCID) difference. In other words: What pain relief do we need to achieve before we decide to implement a new treatment, considering possible side effects and resource allocation?

15. (Being European myself) I agree that your eligibility criteria for sucrose should be liberalized. From the study point of view though, it’s lucky that none of the included infants received sucrose. This would only have confounded your results and the interpretation (p. 16 – 17). The authors might want to rewrite this part of the discussion and also the conclusion. If this study failed to show any benefits of Ametop without sugar, I can’t see how adding sugar could give any better answer to the question whether Ametop relieves PICC-inserting-pain.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.