Author's response to reviews

Title: Efficacy of ambroxol lozenges for pharyngitis: a meta-analysis

Authors:

Jean-Francois Chenot (jchenot@uni-greifswald.de)
Peter Weber (weber.peter@gmx.net)
Tim Friede (tim.friede@med.uni-goettingen.de)

Version: 2 Date: 28 November 2012

Author's response to reviews: see over
Editorial Requirements:

PRISMA: Please confirm in your covering letter that your study adheres to the PRISMA guidelines for systematic reviews (http://www.prisma-statement.org/), and add a statement to that effect in the revised manuscript.

MOOSE: Please confirm in your covering letter that your study adheres to the MOOSE guidelines on meta-analyses, (http://www.consort-statement.org/resources/downloads/other-instruments/) and add a statement to that effect in the revised manuscript.

We went again through the PRISMA-checklist and believe that we have fulfilled all criteria and state so in the revised manuscript. The MOOSE guideline refers to Meta-analysis of Observational Studies in Epidemiology and does not apply to our meta-analysis of RCTs. However we added some items stipulated by MOOSE and not by PRISMA. The suggested items are similar to the PRISMA-checklist and we believe that we comply with most applicable stipulations. We have added some additional information referring to quality assessment and qualification of the researchers not required from PRISMA.

Authors' Comments

Reviewer: Taixiang Wu

Reviewer's report:
1. In the Data Source section, the term “Cochrane Data base of systematic reviews” is not exactly correct, it should be “the CENTRAL of Cochrane Data Base of systematic reviews”;

We have corrected that.

2. A writing skill problem: the expected outcomes of the meta-analysis should be described in the methods rather than in the “Results” section directly, but after that list the results in the “Results” section. This means that what outcomes were planned to be assessed by the meta-analysis, and then what were the results. Thus, this is the description logic.

We have move the description of the outcomes to the method section.

2. Table 2: Jadas score should be Jadad score

We have erased the reporting of the Jadad-Score now, as you suggested.

A question about the methodology issue: the author stated that “We used the Cochrane Collaboration tool for assessment of the risk of bias”. However, the Jadad score was used.

We reported both, but have erased the Jadad-score now.

We have known that there seven points in the Cochrane methods (six points are showing in the table 2, the remain one point is “free from selective reporting”), but the Jadad score has three points only and the total scores is five (randomization, blinding, loss of follow-up). So, how the 4 scores was rated by Jadad score? Please specify in detail in the text.
By the way, the Cochrane Handbook did not recommend the Jadad score. How do you think about it? I would suggest you use the Risk of bias, rather than the Jadad score.

_We have added the Jadad-score since it used to be a frequently used tool. The dichotomous Jadad-score is either to conservative or is inflating the quality since it doesn’t allow uncertainty unlike the Cochrane Collaboration tool for assessment of the risk of bias. Therefore we erased the Jadad-score now._

4. “…..tool for assessment of the risk of bias [7]. We used a fixed-effect model to combine….”. Please get a space there.

_We have done that_

5. I would suggest put figure 2 and figure 3 in a forest plot together rather than separated two figures, similar as two subgroup analysis, conduct a Subtotal but not Total.

_As you suggested we have put figure 1 and 2 in one forest plot._

_Reviewer:_ Christian de Mey

_Reviewer’s report:_

The publication "Efficacy of ambroxol lozenges for pharyngitis: a meta-analysis" by Chenot JF et al. describes a meta-analysis of published efficacy data re. the efficacy of ambroxol lozenges in the treatment of acute sore throat. 14 potentially relevant publications were initially identified; five relevant RCTs reported in three publications were retained (1,772 evaluable patients in total). All relevant RCTs and their core data had already been reported in reference 12, albeit that this did not present a pooled analysis of the data. Based on a pooled analysis of the time weighted change of the pain scores from pre-dose baseline (primary criterion), the overall difference vs. placebo was presently estimated to be -0.11 (CI95 [-0.15; -0.07]) for 20 mg and -0.17 (CI95 [-0.24; -0.10]) for 30 mg of ambroxol. Based on the CONSORT criteria for reporting of parallel-group clinical trials, the quality of reporting of the data was considered to be low. Based on their evaluations, the authors conclude that “although ambroxol seems to be more effective in relieving pain in acute pharyngitis than mint flavored lozenges the effect appears to be small”. Additionally, the authors conclude that “over the counter analgesic medications might be a better option”.

This analysis is affected by several issues – in the following only a few examples are cited (major issues):

- The outcome measures of the fifth trial, although extensively reported in reference 12, were not transferred correctly into the meta-analysis – this has not a large impact, but nevertheless illustrates the lack of methodological robustness of the present publication.

_We agree that the placebo group had 246 participants instead of 236; we have corrected that in Figure 2. This had no impact on the results._

- The primary criterion is reported to have been based on pain scores by means of a visual analogue scale; the source publications leave no doubt that pain was scored by means of a verbal rating scale.

_We have corrected that._
- Table 1 erroneously reports that placebo, ambroxol-20, ambroxol-30, and benzocaine were investigated in trial no. 5; ref 12 leaves no doubt that ambroxol-30 was not investigated in this trial.

*We have corrected that mistake.*

- The publication suggests that more than 50% pain reduction was also achieved with placebo (sucking a mint-flavoured lozenge); such statement is meaningless unless referring to a treatment comparison of the frequency of patients achieving at least 50% pain reduction; no such data were reported in any of the cited publications – see also below. Instead, percentages of patients with overall efficacy scores had been presented in Ref 12 in addition to the primary outcome measure.

*We agree that the statement as we made it in the conclusion might be misleading. Since it is not possible to conduct a blinded trial for sucking a candy versus not sucking a candy the question of the efficacy of sucking non-medical candies will never be resolved. We now make clear that this refers to baseline in the conclusion as we did in the discussion further up. We believe this is an important message that patients can expect 50% pain reduction from baseline by sucking menthol lozenges. We commented extensively that menthol lozenges are most likely not a placebo.*