Author’s response to reviews

Title: S-carboxymethylcysteine in the treatment of glue ear: quantitative systematic review

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PDF covering letter
S-carboxymethylcysteine in the treatment of glue ear: quantitative systematic review

We would like to start by thanking the referees for their hard work. We think the paper is improved because of this, and we have made alterations especially in areas where the terseness of the language was losing readers. This wasn't made any easier by my uploading an interim rather than final version of corrections at the last attempt. Not BioMed fault, but mine because I saved it to a different file here.

Reply to referees

Ian Williamson

We have made the alteration to make it clear that otitis media with effusion is being looked at.

We have simplified the introductory paragraphs to concentrate on rates of bilateral glue ear.

Chris Cates

1 Done

2 Pooling of results to calculate NNTs was not by pooling the risk differences from each trial and taking the inverse of the pooled risk difference as the pooled NNT, but rather from the sum of all events and patients for treatment and placebo. This is now explicit. The method we use obviously weights by trial size rather than variance.

Does it make a difference? Our calculation for pooled NNT gives 5.5 (3.8-9.8). If we use RevMan odds ratios using fixed effects it is possible to calculate 5.5 (3.4-12), or relative risk with fixed effects as 6.0 (3.3-14) or relative risk with random effects as 7.0 (3.6-19).

Which is right, or is it possible to define which is right? This is actually quite interesting, and when we first put our calculator together this was discussed in depth, and consensus at the time was that the method we used was right. But Chris raises an interesting point about proving that, and that will involve choosing some examples, and going back to basics. When people like Altman and Senn can disagree in print over appropriate use of odds ratios and relative risk (BMJ in 1998) us ordinary mortals will have a difficult time of it.
We are as satisfied as we can be that the method we used is correct, and it should now be as explicit as Chris wants. We will undertake to discuss this with our mathematicians and see if there is an answer we can generate from first principles, and we will keep Chris in the loop.

3 We have added more words on the use of L'Abbé plots for examining heterogeneity, with a reference, and discuss it.

Matthias Egger

Matthias was not happy that we had responded to his comments. I thought we had, but am happy to try again.

1 As far as I can see, the only point on which we fail any QUORUM element is that we do not say how many papers we may have though vaguely important, but on examining the abstracts realised definitely had no relevance. All papers that were possibly relevant were retrieved, translated, read, and their fate recorded as included or excluded, and details or reasons given. I can't make that fit the flow diagram (which anyway I fail to understand), but all relevant information has been in the paper from the first draft. Let's not forget that these are guidelines. Let's not also forget that we have in the past been required by journals to perform heterogeneity tests and funnel plots, which were later proved to be wrong or misleading or both. Perhaps the editor can adjudicate on this.

2 The introduction has been simplified.

3 We now specifically explain how improvement was defined using the Taylor paper as an example. What constitutes improvement is explicit

"We were interested in outcomes (including adverse effects) for children, or failing that for individual ears, which could be interpreted as saving a child from an operation for grommet insertion. Ideally this would be a tympanogram type B becoming type A. Where this was not available (because several studies were quite old) we chose outcomes which would today influence the making of the clinical decision not to operate. Definitions used were:

A normal tympanogram
Reversion to normal audiometry
Normal otoscopic findings
Parental view (improvement/lack of problem)."

4 The scoring system used has been shown on several referenced occasions to differentiate between trials where bias is likely to occur and those where it is
not. As is validity, intention to treat versus per protocol, and size. We have performed sensitivity analysis to show that, by and large, the result is robust.

5 There are only seven trials, five of which are small with fewer than 50 patients in whom random factors would be expected to be large. Agonising over details of trial reporting would be a futile exercise.

6/7 We now give a plot of the relative risk of individual studies, and an additional file with all the detailed numbers and calculations for each individual trail. The difference between studies is simple an issue of size and the random play of chance. We reference this.

8 Though we dislike the idea of a combined relative benefit used to calculate an NNT, we have done two things to address Matthias' comments. First we show that the overall rate of events with placebo (baseline risk) is similar to contemporary British experience. Second, we provide NNTs over a range of baseline risk found in the UK, and tie that into the argument about cost-effectiveness. Matthias’ concern that we have little experience outside acute pain can be addressed by reference to our website (www.jr2.ox.ac.uk/Bandolier/painres/PRintro.html); he should be reassured. Our experience is wide, and we have been involved in methodological development.

9 The Porru trial has that data available that was useable based on our inclusion criteria. We decided to include it. If we exclude papers with fewer than 10 patients per group we have been criticised for that. If we include them we get criticised. All the information is available in the tables for anyone to make their own assessment if they so want.

10 The Commins paper is published. The offending sentence will be removed.