Author's response to reviews

Title: The Prevention of Anaphylactoid Reactions to Iodinated Radiological Contrast Media: A Systematic Review of Randomised Controlled Trials

Authors:

Anthony Delaney (adelaney@med.usyd.edu.au)
Andrew Carter (andrewccarter@yahoo.com.au)
Malcolm Fisher (mfisher@med.usyd.edu.au)

Version: 2 Date: 6 April 2006

Author's response to reviews: see over
Dear Biomed Central Editorial team and Reviewers.

We would like to thank the editors and referees for taking the time to review our manuscript. Specific responses to the comments are attached below and have been highlighted in the revised manuscript.

Reviewer 1.

General

Dr. Delaney’s article is a systematic review of the use of H1 antihistamines and steroids prior to iodinated radiological contrast media administration. While Dr. Delaney’s methods are thorough and transparent, I do not believe his analysis of the data support his conclusions. In particular, I worry about the heterogeneity of the data and the lack of high quality randomized trials on which he bases his conclusions.

We agree quite strongly with Dr Liu’s general comment about the heterogeneity and lack of high quality randomised trials that form the basis of this review. One of the primary reasons for producing this review is to document the current state of evidence that addresses this topic using thorough, transparent methods. By understanding the limitations of the evidence available, we can inform clinicians’ decisions, so that they are aware of the limitations to the evidence that is currently guiding clinical practice, and hopefully point out areas where research may be able to further this knowledge and improve patient care. We think that a thorough systematic review that points out these deficiencies is an important stepping-stone to improving knowledge. The refinements that have been made to the document based upon the insightful comments of both reviewers, should clarify these objectives and lead to an improved manuscript.
Page 2: The analysis for H1 blockers should not include the study from Ring et. al, unless that paper separated the patients receiving only H1 blockers. In that study, some patients received steroids, and some received more than one anti-histamine. Dr. Delaney should mention if they only analyzed the subset receiving clemastin alone.

The study by ring included four separate groups, one of which received only clemastine. This group was included in the pooled analysis for H1 antihistamines, and this distinction has been clarified in the results section. The combined H1 and H2 group is mentioned separately in the results.

Page 3: Dr. Delaney’s conclusion that “methylprednisolone 32mg be given at least 6 hours prior and two hours prior to the administration of contrast” is based on one study alone – please see later comments for page 12 and 13.

See below.

Page 4: The author needs to elaborate on the difference in allergic reactions between non-ionic and ionic contrast agents. The numbers he quotes for the difference between the two types of contrast agents would suggest that using non-ionic contrast agents reduces the risk of allergic reactions more than the interventions he is studying. One might wonder if his meta-analysis should focus more on the difference between non-ionic and ionic contrast agents rather than pre-medication in the prevention of allergic reactions.

Whether the reduction in allergic type reactions with the use of non-ionic contrast is of a similar or greater magnitude than the reduction that is seen with the use of anti-histamine pretreatment is an interesting question and may be the basis for a separate study. The additive effects of using both non-ionic and prophylactic medication has to our knowledge, not been formally studied in high quality prospective trials apart from the Lasser study that we have included, which as noted was underpowered to detect a clinically important difference in serious reactions. The focus of this study was to examine the evidence for the use of prophylactic medications to prevent allergic type reactions to all types of iodinated radiological contrast. As antihistamines and corticosteroids are being recommended as prophylactic treatment, we thought it important to examine the basis for these recommendations.
Page 9: The author mentions that only one study clearly met all of the predefined validity criteria. In fact, at least two of the studies included in the meta-analysis met NONE of the validity criteria. Given that these studies are not deemed to be of high quality based on these criteria, shouldn’t they be excluded from the meta-analysis? Excluding the low quality studies seems reasonable, but that leaves too few studies to analyze. Therein lies the problem with this meta-analysis – there are too many poor quality studies with too much heterogeneity to make any sound conclusions.

We agree once again with Dr Liu to an extent regarding the quality of the studies that were included in this review. One of the important findings of this systematic review is to point out the limitations of the current evidence that is being used to guide clinical practice. We feel that this is a strength, rather than a weakness of this review. When “opinion is divided” as to the value of using preventative medications, it is important to demonstrate the basis of this evidence rather than simply offering another opinion. This transparent and thorough examination can then form the foundation for a more rigorous examination so that future clinicians and their patients can have more certainty as to the optimal treatment.

Page 9: Dr. Delaney states that there is “significant heterogeneity amongst the included studies….it was not possible to explore further reasons for the heterogeneity.” I think it would be important for Dr. Delaney to elaborate on this more. Could he in the discussion, describe exactly what was heterogeneous between the studies, and whether there should be a standard for future studies? If there should be a standard, what should be tested?

There was significant clinical heterogeneity apparent in the studies of H1 antagonists, specifically different agents, with differing doses and timing. There were also differing contrast agents used, and the populations being studied were different. The fact that the test for heterogeneity was significant confirmed that these differences were statistically significant. The reasons for this heterogeneity are presented in Table 1, and we have added this to the discussion section to make it clearer what the heterogeneity in this study may have been due to.

Page 12: “strongly suggestive of a protective effect of corticosteroids.” I’m not sure how the author can come to this conclusion when there were not enough studies to analyze. His conclusion is based on only one trial, and that is not sufficient for a meta-analysis.

While there is still some debate about whether a single high quality, adequately powered RCT provides better evidence than a meta-analysis of smaller RCTs, we would accept the proposition that “strongly” may overstate the conclusions that can be drawn from these data, and have adjusted the manuscript accordingly.
Page 12: “The protective effect of H1 antihistamines and corticosteroids in high-risk patients has been demonstrated in non-randomized studies.” In the absence of good randomized data, data from non-randomized studies needs to be elaborated on (probably in the background section).

Again, most authorities would regard evidence from non-randomized studies to be less robust and more prone to biases than well conducted randomized studies, and so is less preferable under most circumstances. There may be circumstances, such as for outcomes that are important but rare (in this case severe anaphylaxis with contrast media) where well-conducted observational studies have an important role to play in illuminating the answer to a research question. We have chosen to elaborate on the existing non-randomized studies in the discussion section, on page 12/13.

Page 13: “the results of this review would suggest that two doses of corticosteroids be used as prophylaxis, especially in light of the results of the Lasser study...” As mentioned previously on Page 12, conclusions of a meta-analysis should not be based on one trial, in this case the Lasser trial.

See Below

Page 14: Conclusions: Once again, I don’t think the authors can conclude that their meta-analysis shows that the use of steroids is supported by available trials, especially when there was only one good quality trial that they are basing this conclusion on. In addition, the heterogeneity of the trials makes it impossible to support the routine use of H1 and corticosteroids without further studies.

See below.

Discussion: I think that the author should state that more high quality studies are necessary before any meta-analysis conclusions can be made, and describe what he thinks these future studies should look like.

We agree with Dr Liu think that this is one of the most important findings of this study is that further research is needed, as the current recommendations are based upon a limited number of poorly conducted studies, in populations receiving contrast agents that are not commonly used any more. We have elaborated on this issue in the discussion. The conclusions have been clarified to reflect this concern more closely.

Page 4, line 7: Spelled “focused” wrong.
This has been corrected
Page 7: The author should indicate what he means by “pseudo-randomized” and why he allowed pseudo-randomized trials to be included in the analysis.
As is done in the Cochrane Collaboration, studies that use a method of randomization that does not preserve allocation concealment (such as medical record numbers, date of birth or days of the week) were included. These studies are referred to as pseudo-randomized, as it is possible to predict in advance which group the patient will be allocated to, and so introduces the possibility of selection bias. To remove this confusion, we have simplified the description of the inclusion criteria and added an explanation of this to the methods section describing the validity assessment of the included studies.

Page 4: The background section should focus more on the morbidity and mortality of contrast agents. There is a recent article published that describes some U.S. statistics:
x-ray contrast media on u.s. death certificates.
PMID: 16498085 [PubMed - in process]

We would like to thank Dr Liu for bringing this reference to our attention. We believe it highlights the need for at least well designed prospective studies to delineate the risks associated with the use of contrast media and have added the reference to the discussion regarding the potential direction of future research projects.

Page 4: It would be interesting to have a description of the spectrum of allergic reactions that can occur with contrast agents in the background section.
We have added some discussion of the possible mechanisms for allergic type reactions and the spectrum of this problem to the introduction.
Reviewer 2

1. In the abstract and text the authors should clearly state that the 4 studies examining the use of H1-antihistamines were all based on exposure to ionic contrast material. They should also clearly state that no studies using nonionic contrast material survived their eligibility for inclusion in this study. As most contrast studies today are nonionic this distinction is important. This point is well made by Dr Cochran we have made attempted to clarify this in the text and abstract.

2. Lasser’s studies included all adverse reaction which included anaphylactoid reactions and chemotoxic reactions (for which steroid pre-treatment would not be expected to be helpful. The authors’ conclusions about steroids pretreatment is based on Lasser’s studies. The conclusions should be modified to reflect this. This point is also well made. We have included a description of the types of reactions in table one so that readers can identify the types of reactions that were examined in Dr Lasser’s studies. We have addressed this point in the discussion.

We would like to thank both reviewers once again for taking the time to review our manuscript. We agree that the overall strength of the evidence available to help guide clinicians in this area is less than optimal. However, the reason we believe that this review is important, is that rather than simply noting that opinion is divided as to the optimal method of preventing anaphylactoid reactions to iodinated contrast media, this systematic review addresses a specific question, using thorough and reproducible methods. The results of this study can then not only inform clinicians of the levels of evidence that current recommendations are based upon, but also point out the gaps in the current knowledge base so that future research can address these deficiencies. We are grateful for the insightful comments offered by the reviewers and think that the changes made have led to an improved manuscript.

We look forward to your decision regarding publication and if there are any further queries that we can answer in the interim please don’t hesitate to contact me.

Sincerely

Anthony Delaney.