16-Jul-2017

Dear Dr. Sadeghirad,

Manuscript ID BMJ.2017.039974 entitled "Corticosteroids for treatment of sore throat: a systematic review and meta-analysis of randomised trials"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We are interested in proceeding with this paper and hope that you are willing and able to revise it in response to editorial and reviewer comments. We are looking forward to reading the revised version and reaching a final decision on the paper.

Very truly yours,

Elizabeth Loder, MD, MPH
eloder@bmj.com

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Report from The BMJ's manuscript committee meeting

Present: Jose Merino (chair); Tim Cole (statistician); Helen Macdonald; Rubin Minhas; John Fletcher; Tiago Villanueva; Sophie Cook; Joseph Freer; Daoxin Yin; Michael Mittelman

Decision: Request revisions

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

* Several editors thought the research question was relevant, especially since there is new concern about the safety of NSAIDs and a desire to avoid the use of antibiotics when appropriate.

* On the other hand, there was a great deal of concern about medicalisation of sore throat. Several editors suggested that self-management of mild sore throat is the goal of most primary care clinicians. You might emphasise that the majority of these studies come from an ED setting, where presumably most patients had sore throats severe enough to cause them to seek such treatment.

* There also was worry about potential side effects of corticosteroids. We would like you to provide more information about exactly how side effects were queried or sought in each of the included studies. Please also comment on the possibility that longer term side effects or side effects related to frequent episodic use of steroids might have been missed in these studies.

* Please also make clearer, perhaps in the abstract, what dose and drug and route was most commonly used in the studies. Several people mentioned that they read the entire review without having any idea what was meant by a single dose of steroids. Which steroid? Which dose? Parenteral or oral? It is not until one gets to the table that this is clear.

* There was worry that busy doctors might forget that it was a single dose in most of these studies and end up prescribing a medol dosepak, or refilling steroids over the telephone for patients whose symptoms continue. We thought this should be addressed and discouraged in the accompanying education piece.

* We would also like more detail on the therapy in the control conditions. What is treatment as usual? Which patients got other pain therapy?

* Several editors felt this didn't add much to the 2014 Cochrane review. Can you elaborate on why this does add?

* We were very concerned about the reviewer who pointed out the 2003 paper that should not have been picked up if the bridging search in fact began in 2010. Can you reassure us about this matter?

* We felt that the conclusion was overly positive given the lack of evidence about harms and that it would be more appropriate to say that the balance of benefits / harms is not well enough established.

* We wondered about generalisability since the review excluded patients most likely to have very severe sore throat, e.g. those with mononucleosis, post-intubation, etc.

* Our statistician commented "Negative CIs the wrong way round -1.9 to -7.8, make them positive."

* We would like more information on why you excluded studies of children under 5 years?

* Highly significant IM vs oral corticosteroid interaction, but between rather than within studies.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
This is a very detailed review on the use of corticosteroids in söre throat. The possible adverse effect of gastrointestinal bleeding still seems to be a problem in the use of corticosteroids for pain relief in söre throat. Lozenges containing flurbiprofen may be a good alternative to corticosteriods for söre throat pain.
The manuscript may be accepted for publication as it is.

Additional Questions:
Please enter your name: Selcuk Mistik

Job Title: Prof. Dr.

Institution: Erciyes University Medical Faculty

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
We commend the authors on a very well written and rigorously researched manuscript that may have important implications on the treatment of sore throats using corticosteroids.

I think there are few things that require some clarifications that would strengthen this manuscript.

1. The value of any intervention (i.e. steroids in this case) must balance benefits and potential harms. The meta-analysis of RCTs does a nice job of summarizing potential benefits of steroids in this situation. Although the authors also summarize harms from each study, it is well known that harms of interventions are often poorly ascertained by RCTs for several reasons. It would be worthwhile for authors to note possible under-ascertainment of harms in the discussion and supplement with any data re: harms from observational studies in this patient population.
a. The authors include one reference #33, which recently evaluated harms of steroids using a large database; however, they minimize the impact of these results, citing concerns of confounding by indication, differences in doses, and differences in duration. While some of these are valid concerns, it should be noted that the concerns about confounding by indication were recently addressed by recent letter to editor. If authors agree with rebuttal, they might use data from this study as one observational study to report steroid harms.

3. As pointed out by the authors, there were significant biases associated with many studies. Given this limitation, conclusions of benefits should likely be more tempered.

4. The I2 for most outcomes suggested significant statistical heterogeneity, which makes pooling of results difficult to interpret. Authors could further evaluate this heterogeneity with sensitivity analyses to see if this could reduce heterogeneity. This should also be discussed as a limitation of the meta-analysis in the discussion section.

5. The quality assessment and limitations (both within-study and between-study) should be expanded, as this is one of the most important aspects of a meta-analysis.

6. Emphasize the need for high quality data to show true value on this topic.

Minor comments:
1. On page 3 the hyperlink to MAGICapp appears to be user protected. May consider mentioning that or reference it in the reference section.

2. In Table 1, Hayward should be associated with Reference 14 not reference 4.

Additional Questions:
Please enter your name: Akbar Waljee

Job Title: Assistant Professor

Institution: University of Michigan

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 3

Recommendation:

Comments:
Thank you for asking me to review this manuscript.
Essentially this is an update to the systematic review of the same name published in the BMJ and later in the Cochrane Library, with last update on October 2012. Since this publication, one large new RCT has been published. The introduction states that this review is part of a new program from a commercial group called MAGIC, and has apparently already been published as a guideline (though I was not able to access the link on Line 47), so perhaps this is still to occur.

The manuscript uses typical systematic review methods to search for, select and synthesize eligible trials. The authors performed a bridging search from 2010 to present, and identified the one new trial (Hayward et al) as noted above. However, I note that the authors also identified a trial of Ahn et al 2003 which had been identified and excluded as not being eligible in the Cochrane review. This raises 2 questions, first how was this paper identified if the current manuscript's search only extended back to 2010? I don't see from their methods section that this trial could have been picked up. Second, the Cochrane review authors excluded this paper as it was not a randomized controlled trial. While I have only access to the English abstract of this Korean language paper, this states ''The 109 patients were arbitrarily divided into 3 groups and each group was prescribed different combinations of oral steroid and NSAIDS.'' It is unclear to me how this previously excluded paper would have been identified, and why it would have been included? Did the authors find out additional information from the authors that this was indeed an RCT?
In the discussion section the authors noted that inclusion of the 2 "new" papers doubled the number of participants. In fact it was really only the Hayward et al trial which added substantial numbers to this, the small Ahn study (which likely should not have been included) added 72 patients. Certainly the Hayward paper adds considerably to the systematic review, both in numbers of participants, also the setting ie general practice, and the use/not use of concurrent antibiotics. These latter aspects were indeed why the Hayward trial was justified.

I am unclear what the value of the patient panel was to this study. In the discussion it claims that the panel considered additional outcomes that the participating patients considered important including recurrence, or days missed from school or work. However, some of these outcomes were clearly listed in the Cochrane review – in what way therefore did the patient panel change the planned methods?

The conclusions of the study, final paragraph, seem to make generalizations not supported by the evidence. 'many patients are likely to consider them important' – what is the basis for this statement? And that 'adverse effects are rare or absent' - again would agree for the 'serious adverse effects' part of this sentence, but there is evidence of adverse effects of steroids so these statements do not quite seem correct.
I guess the question is whether the addition of a new trial justifies a new protocol, review process and publication? Certainly the new large trial is important for this area and reduces summary effect size, while increasing generalizability to primary care settings. The authors don't really comment also on the issue of how readers should interpret the findings of a systematic review when a large well conducted (essentially negative) new RCT trial has somewhat different findings from the smaller (more methodically flawed) studies that showed a small significant effect - what should the clinician 'trust' the most here?
Some minor typos - the included author Kiderman is misspelt throughout (as Kinderman), and the year of the O'Brien 1993 paper is incorrectly noted as 1994 . This link did not workhttps://www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn

Additional Questions:
Please enter your name: Matthew Thompson

Job Title: Professor and Vice Chair for Research

Institution: Dept Family Medicine, University of Washington, Seattle

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: I was previously funded under the TOAST trial which is included in the current systematic review, but not for about 3 years.
I have provided consulting for Roche Molecular Diagnostics, who make point of care tests including for group A strep.

Reviewer: 4

Recommendation:

Comments:
1. GENERAL COMMENTS.
This meta-analysis from B. Sadeghirad and coworkers on "Corticosteroids for treatment of sore throat provides an important level of evidence (Ia) and clear recommendations for the use of single low (up to 10mg) doses of systemic corticosteroids to treat sore throat in the context of acute tonsillitis, pharyngitis and the sore throat syndrome in children older than 5 years and adults. The overall and subgroup analyses are well done and the conclusions and recommendations based on the studies analyzed in the meta-analysis.

2. COMMENTS ON SPECIFIC SECTIONS:
Abstract
- Page 2 (Results). The maximal dose of steroid (10mg) should be identified here (line 31). The last sentence "None of the …" is too categorical since some adverse affects have been reported in the different studies. It should be softened by something like "probably".
- Page 2 (Conclusion). A meta-analysis cannot provide cause-effect conclusions but recommendations. Thus, the word "provide" should be changed by, for example, by "is recommended".
• Methods
- Page 6 (lines 7-17). It looks like all larger effects in the subgroup analyses are significant when only "parenteral versus oral" (Appendix 4) is significant. This should be clarified. It is clearly stated in the discussion section (page 10, lines 52-54)
• Results
- Page 7 (lines 17-20). The identification of studies concerning age of participants is not correctly reported (see Table 1): 5 studies are in adults, 3 in children, 1 in both children and adults, and in one the age is not reported. This should be also clarified.
- Table 1 (page 14). In the "dose and duration" column, the box for Betamethasone should report the real dose, in addition to the administered volume.
- Table 2 (page 15). In the "Absolute effect estimates" column, the MD values in the boxes for "Mean time to onset …" and "Mean time to resolution …" should be better presented with a negative value (-) to avoid confusion with the Forest plots in Figures 4 and 5, respectively. In the footnote 5, "now" should be changed to "one".
- Figure 1 (page 21). The main reasons of drop-outs in the box "Articles excluded (N=2303) should be reported".
- Figure 6 (page 26). If the reported reduction of pain is "at 24h" this time should be reported in the figure legend.
- Appendix 3 (page 31) and 4 (page 32). In the P value column, the symbols " *** " or " ** " for small number of trials is confusing since asterisk are usually used for p values. Could they be changed to some kind of abbreviation defined as a table footnote (SNT, small number of trials)
• Discussion
- Page 10 (lines 19-24). The word "reduce" denotes cause-effect. OR / RR from meta-analysis do not provide cause-effect data (this is only given by RCT studies) but association data. All word denoting cause-effect should be changed all over the document (also in page 11, line 44, and in the footnote 13 of Table 2).

Additional Questions:
Please enter your name: Jaoquim Mullol

Job Title: Director, Rhinology Unit & Smell Clinic, ENT Department

Institution: Hospital Clínic - IDIBAPS. Barcelona, Catalonia, Spain

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: Yes

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

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If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: During the last 5 years, Joaquim Mullol has been member of national and international scientific advisory boards (consulting), received fees for lectures, and grants for research projects from ALK-Abelló, Crucell, Esteve, FAES, Genentech-Roche, GSK, Hartington Pharmaceuticals, Hyphens, Johnson & Johnson, MEDA Pharma, Menarini, MSD, Novartis, Sanofi-Genzyme-Regeneron, UCB, and Uriach Group. JM has also received travel reimbursement from several Scientific Societies such AAAAI, EAACI, ERS, and SEAIC.