

Something different from an updating Cochrane systematic review to a published systematic review.

Dear Editor,

We read with interest the currently published systematic review by Manfredini, et al.¹ The authors searched Pubmed (www.pubmed.org) and conducted a systematic review summarizing the current evidence to find the efficacy of hyaluronic acid in treating temporomandibular joint disorders (TMD). And they thought that, based on current evidence, hyaluronic acid injections were not proven superior to other active treatments, and the result seemed inconclusive.

As we are now updating the Cochrane systematic review "Hyaluronate for Temporomandibular Joint Disorders,"² we have found something other than this systematic review.

Firstly, we think that this systematic review has some selection bias. The authors only searched Pubmed for English papers and found that 19 articles met the inclusion criteria, with only eight randomized controlled trials (RCTs) included. We think this is inappropriate. As it is defined, a systematic review is a type of study that focuses on a clinically important question that is hopefully answered by well collected, identified, appraised, and then synthesized high quality studies. This means that the reviewers should try to find all relevant studies through the search, and that searching Pubmed only and limiting the language to English cannot be considered a comprehensive search. We have searched the Cochrane systematic review, and there are at least 12 RCTs, relevant to this topic, published after 1999.

Secondly, we believe that a systematic review should draw conclusions about the effectiveness of the intervention based on evaluation of the validity of the included studies,³ and the validity of the studies should be assessed through risk of bias appraisal. We could not find a critical appraisal of the included studies from the systematic review. Instead, the authors assessed the studies through a structured reading of articles format (PICO format), which has been used to indicate main characteristics being fully reported or not, and is not related to methodological quality. Indeed, methodological quality implies how the unavoidable systematic errors or biases in designing and processing a study have been controlled or reduced and scales, checklists, and

domain-based evaluation should be used as tools to assess the methodological quality.

Thirdly, based on the above two reasons, the conclusions that the authors elicited remained uncertain. Nevertheless, as we expanded the search for critical appraisal of the included studies, we found some credible outcomes with considerable confidence. When updating the Cochrane systematic review, we retrieved 18 RCTs (1985-2010). The preliminary outcome of the meta-analysis showed that hyaluronic acid could significantly relieve the symptoms (number of participants (n)=170, Std. Mean Difference (SMD)=-0.55, 95% confidence interval (95% CI)=[-0.92,-0.19]) and clinical signs (n=319, SMD=0.97, 95% CI=[0.51,1.43]) in short-term (around one month) and long-term (six months) clinical signs (n=129, SMD=0.71, 95% CI=[0.31,1.11]), when compared with negative control (including placebo, arthrocentesis alone, or arthroscopy alone). When compared with corticosteroids, with only short-term data available, hyaluronic acid had a similar effect in relieving symptoms (n=574, SMD=-0.16, 95% CI=[-0.81,0.49]) and clinical signs (n=654, SMD=-0.08, 95% CI=[-0.50,0.66]). Sensitivity analysis (including high-quality RCTs only, exclude studies causing high heterogeneity, etc.) showed that these outcomes were sound.

We think that the present evidence supports application of intra-articular injection of hyaluronate for treatment of temporomandibular disorders (TMD). It might have similar effects with corticosteroids in the short term for TMD.

Chun-jie Li, M.Sc.

Zong-dao Shi, M.D.

West China College of Stomatology
Sichuan University

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And what about clinical evidence? Drs. Daniele Manfredini and Luca Guarda-Nardini's response.

Dear Editor,

It is with pleasure that we accept the editor's invitation to reply to Dr. Li and colleague's letter as an opportunity to specify that, if there is something different from an updating of the Cochrane systematic review to a published systematic review, it is not necessarily true that it is in advantage of the former.

Li and colleagues maintain that our recently published systematic review on the effectiveness of hyaluronic acid for TMJ disorders¹ missed the inclusion of relevant data, which should have changed our conclusions. Our conclusion that much has yet to be done before specific indications and protocols for HA injections can be proposed with good predictability at the individual level was in line with findings from the previous Cochrane review by Shi, et al.² Notwithstanding, it seems that during the process of updating their review, Li and colleagues found many more articles dealing with RCTs on HA injections for TMJ disorders with respect to our "PubMed-restricted" search. Leaving aside the curious suggestion by Li and colleagues on how a systematic review should be performed, since accustomed authors must know that the final published systematic review in a high-quality peer-reviewed journal is often influenced by the reviewers' suggestions,^{3,4} we gratefully thank the authors for allowing us to read their updated review to get a basis for our reply. However, we had no doubt that all supposedly missing papers came from non-mainstream literature. Indeed, the references we are talking about are all (N=8) from Chinese authors, mostly published in their country's journals and language. None of the journals is included in the ISI list of medical periodicals with an official impact factor. In synthesis, such papers represent part of the multitude of articles published yearly all around the world in dental magazines, and Li and colleagues should be surprised in discovering the number of similar papers in German, Spanish, Italian, Portuguese, Japanese, French, and Swedish languages, just to mention the most accessible ones. The arbitrary selective inclusion of the authors' native literature, along with the (forced for obvious reasons of unfamiliarity with foreign languages and periodicals) exclusion of all the other non-mainstream papers, is a major

selection bias, which actually undermines the validity of the updated review's conclusions. It is indeed our firm belief that all academicians involved in highly impactful projects throughout the world have the duty to submit their works to widely diffused international journals, because that's the only way to share findings with the community of researchers. So, we will be more than happy to re-appraise and re-appreciate the external validity of the literature cited by Li and colleagues as soon as the authors of the single papers will make these papers available to the international community.

Apart from these methodological considerations, the most striking point of criticism with respect to Li and colleague's letter is that they appear to contradict themselves in the abstract-conclusion section of their updated review⁵, by stating that "There is now some evidence to support the effect and safety of hyaluronate for treating patients with TMD. Further high quality RCTs on hyaluronate need to be conducted to confirm the evidence." The second sentence of the statement is absolutely in line with our PubMed systematic review. I So, the question is: from where does this "some evidence" come from? Hyaluronate was superior to negative controls, and this is nothing new in the TMD literature, which has plenty of examples showing the effectiveness of most treatment approaches.⁶ No meta-analytic findings could be provided as for HA vs. arthrocentesis or other treatments. Also, based on three papers (two of which were from native literature) hyaluronate was judged equal to corticosteroids in the short-term and slightly better for long-term (six-months!) results on clinical signs such as joint noises, which is another quite obvious finding due to the lubricating effect of HA. In a clinical setting, it must be remembered that joint noises are not pathological markers *per se*⁷, and basing a treatment indication/effect on their presumptive reduction is clinical nonsense.

While not underestimating their strong effort to perform their Cochrane review and with full respect for their opinion, Li and colleagues are strongly encouraged to consider that a "published" review has to provide answers to clinically relevant questions that may fall outside the boundaries of statistics: how, when, why, and with which protocol (i.e., low-medium-high molecular weight HA; one-three-five injections; with or without additional arthrocentesis) a hyaluronate-based treatment

must be prescribed? "It seems that, on these premises, there is still no clear evidence of the superiority of any injection protocol over the others, and that much more research is needed to offer our patients the best possible treatment option at the individual level . . ." that is the conclusion of a "published review" with PICO-like assessment of the papers.

Respectfully,
 Daniele Manfredini, D.D.S.
 Luca Guarda-Nardini, M.D., D.D.S.,
 University of Padova, Italy

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Letter to Dr. Brenkert re: his article in the October 2010 issue of CRANIO

Dear Dr. Brenkert,

Thank you for the great article, and you are bang on with your comments about radiographic imaging to Dr. Spahl. The literature is quite clear on this and has been for 30 years or more. I would like to recommend the Damon system to you for such TMD cases. I am getting much more accurate posterior torque control with ensuing occlusal [perfection] than ever before. I have validated this, to my own satisfaction at least, with "T-Scan." I just presented information to an advanced Damon users group in Calgary, Alberta, Canada, which showed that other orthodontic systems have an accuracy of tooth placement of 0.4 mm; Damon is 0.1 mm. Damon is now the standard of care, especially in advanced TMJ cases. Please note, however, that Damon is not a new bracket per se; it is a system, and as such, needs many hours of advanced training. It is not for the neophyte.

Regards,

Andrew Thompson, B.D.S., D.D.S., D.Ortho.
 Parklane Dental Specialists
 Halifax, Nova Scotia