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Inappropriate use of meta-analysis in an evidence-based assessment of the clinical guidelines for replanted avulsed teeth. Timing of pulp extirpation, splinting periods and prescription of systemic antibiotics

LETTER TO THE EDITOR

The use of evidence-based assessment of dental trauma treatment procedures is in high demand and three studies have lately been published in dental traumatology all relating to replantation of avulsed teeth (1–3). A very extensive work has been carried out by the authors to track down all the clinical evidence behind recent treatment procedures and they should be complimented for their work. In the extensive search performed, a handful of non-randomized studies were found for each subject. To analyse these studies, meta-analyses were performed. Does performing a meta-analysis automatically mean that the assessment is evidence-based? In our opinion, this is not enough. For a meta-analysis to be valid, several factors need to be considered. The meta-analysis has to be a part of a systematic review. We mean here a collection of all relevant evidence based on *pre-specified eligibility criteria*. The systematic review should aim at minimizing the risk of bias by using a protocol and transparent systematic methods (4, 5). Hinckfuss & Messer do not clearly state that their reviews were based on protocols with pre-specified methods.

Another issue is that any conclusion drawn based on reviews and meta-analyses are only as valid as the included studies. If there is a high risk of bias in the included studies, there is also a high risk of bias in the summation of the studies and the meta-analysis. Because of this, the appraisal of the risk of bias is a key element in performing a systematic review. Hinckfuss & Messer state that such an appraisal has been performed; however, for the reader of the reviews, this is not enough, the results of these assessments need to be reported explicitly in the publication of the review allowing the reader to make his/her own informed decisions.

A further limitation of the studies performed by Hinckfuss & Messer is that the results are based on non-randomized studies. It has been shown that non-randomized studies are very prone to bias (4). When addressing effects of health care, the most appropriate study design is the randomized controlled trial, because randomization is aimed at distributing the prognostic factors even among the different groups. As an example for the outcome of PDL healing, an important prognostic factor is dry extraoral time before replantation.

None of the included studies controls for this factor. There is no guarantee that the patient groups examined in the various studies are in anyway homogeneous with regard to the length of extraoral time. The outcome of each study will therefore be strongly influenced by the number of cases with long or short extraoral times in the patient material. Randomization also minimizes the risk of selection bias, as the choice of treatment is not based on prognostic factors. In the studies included by Hinckfuss & Messer, there is a high risk of selection bias as the decisions for giving or not giving antibiotics in the various are not clear. Several possibilities come to mind:

1. Antibiotics are administered to patients with an increased risk of infection due to contamination of the tooth by contact with soil, or long extraoral dry time.
2. Antibiotics have not been administered to patients where the tooth has not left the oral cavity and therefore has a reduced risk of infection.
3. Lack of compliance with existing local treatment guidelines

In situations 1 and 2, a serious selection bias is the expected result and under-and over-scoring respectively of the effect of antibiotic is the likely outcome. No relevant information about the selection criteria's is present in any of the cited studies. Similar problems are present in the case of splinting time. The recorded splinting times will be potentially influenced and biased by the use of long-term splinting for complicated cases.

Based on the above-mentioned limitations of the studies, the results should be interpreted with caution. Due to the lack of reporting on the risk of bias in the included studies and the non-randomized design of the studies, performing a meta-analysis might not be wise as one runs the risk of getting a result that is truly not valid, but appears to be very precise. It is also not clear whether the studies are similar enough to warrant a meta-analysis; if the studies are clinically heterogeneous, a meta-analysis is not applicable. Finally, the inclusion of a study where the no-antibiotic group consists of two

patients makes the pooling of studies not reliable. A similar problem is found in the study 'Timing of pulp extirpation' (Two studies having two or three patients in the experimental groups).

To combine non-comparable materials (the variables examined were not being an essential part of the study) and to use extensive statistics such as odds ratio calculations and study weightings and forest plots do not compensate for the non-comparable nature of the selected articles for the meta-analysis.

If meta-analysis is not applicable, how do we then acquire the needed insight to perform an evidence-based treatment? Performing a systematic review will always be a sound choice even if the studies are too heterogeneous to combine in meta-analysis. A systematic review should provide a careful description of each study including an assessment of the risk of bias. If the included studies are methodological or clinically diverse, a meta-analysis should not be performed, instead the results should be presented in a qualitative synthesis. This is also advised if the included studies have a high risk of bias (4). Performing a systematic review will also make it clear in which areas performing randomized controlled trials are called for. We believe that the only valid conclusion to be drawn by the reviews by Hinckfuss & Messer is that there is no enough evidence at this time to give evidence-based recommendations.

The criticism expressed in this letter is not in any way an attempt to keep people from using meta-analysis in the field of traumatology, as we believe they are of high value when used correctly. However, researchers should be encouraged to use protocols and make their research transparent. We recommend using published reporting guidelines to allow for sufficient critical appraisal of the reviews and the studies used in the review (http://www.equator-network.org).

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RESPONSE FROM THE AUTHORS

The inclusion of studies in each of the 3 papers was based on the criteria listed in Table 1 of each paper.

We agree that non-randomised studies are very prone to bias and that randomised controlled trials provide the highest level of evidence as acknowledged in our papers. However, the ability to conduct a randomised controlled trial on avulsed teeth would be complicated by many uncontrollable variables and it is likely that gaining ethics approval would be difficult. Perhaps prospective cohort studies could be considered the top level of evidence when assessing research for replanted avulsed teeth. The debate over using cohort studies for meta-analysis was mentioned and it should be noted that meta-analyses have been performed using cohort studies in many areas of medicine.

As discussed in the papers the studies were limited by lack of reporting of many details in current research on replanted avulsed teeth. Attention was drawn to the possibility of bias due to lack of random allocation of any of the interventions investigated and as mentioned the random effects model was used to estimate treatment effects more conservatively.

We believe the articles provide evidence to support the current clinical guidelines for the treatment of replanted avulsed teeth although this evidence is not strong. The articles also draw attention to the need for larger samples of teeth and better reporting of samples (details such as extraoral time, tooth maturity, intervention allocation) for data in future research on avulsed teeth.

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