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Response from authors

Dear Editor,

We thank Professor Hargreaves for his interest in our paper.

The McGill scale was used in this study to measure pain at baseline before the procedure was started and then again at 6 and 24 h to measure pain relief from the pulpitis. Because we had not anticipated any more than transient pain from the intra-oral injection itself, the patient's pain level was not measured after the injection. We agree that the McGill scale would not have been a useful instrument in this situation.

Professor Hargreaves queries our use of the term 'significant' to describe the pain after the injection of ketorolac. We agree this is a purely subjective judgement by the clinician involved (Dr Mellor) based on 30 years clinical experience. This was not just pain on actual injection, it was pain that continued until local anaesthetic was given in that area for the procedure itself (in the maxilla) or for the duration of the visit (in the mandible). Patients were not kept beyond the extent of the treatment so the length of time that the post-injection pain lasted was not measured. The study was terminated early by Dr Mellor as he felt unhappy at administering a painful injection when the whole point of the study was to make the procedure more painless. In addition, the successful pulp extirpation rate was no different in the small number of patients treated.

A. C. Mellor[1], M. L. Dorman[2] & N. M. Girdler[3]
[1]*School of Dentistry, The University of Manchester;* [2]*Department of Oral and Maxillofacial Surgery, Sunderland Royal Hospital;* [3]*School of Dental Sciences, University of Newcastle*

Dear Editor

As a general principle I wholeheartedly agree with any plea to interpret study findings with caution. Nevertheless what was presented in this article is a clear, simple statement by researchers that, having tried their test regime on a small number of patients in blinded RCT conditions, they reached the conclusion that it was ethically unacceptable to continue to offer this treatment, and acted upon it. Probably it's not for me to judge whether that was the 'right' decision for them to make – whatever that means – but that is what happened. Professor Hargreaves points out that in his study with Penniston, no patient undergoing an intraoral Ketorolac injection chose to withdraw. It appears that none of Mellor *et al.*'s patients actually withdrew following Ketorolac injection, either, but four of the first five made it clear that this was very unpleasant.

On reading Hargreaves' remarks, my reaction was to ask, just how far is the statistical reviewer role meant to extend? I don't think the onus should have been on me to find out that the McGill pain scale may have limited sensitivity, still less to systematically review the evidence in favour of Ketorolac in a variety of contexts. I'm all in favour, in principle, of the idea that articles

should include systematic reviews of existing evidence. At a recent meeting Iain Chalmers gave a brilliant exposition of this point, which was one of the late Archie Cochrane's most important contributions to epidemiological thought. Nevertheless it's a big onus to place on researchers, let alone referees. My comments referred solely to the evidence provided by this single study. I believe this is normal practice, especially when a referee such as a statistician reviews an article for a clinical specialty in which inevitably he has limited knowledge and familiarity with the literature. Clearly it is necessary for someone to fit the pieces of evidence together. Nevertheless I reckon it was right for us to record the fact that one research study concluded that this treatment, given in this precise way, was unacceptable (albeit in the short term) to patients – in other words, that the investigators felt it was no longer ethical to randomise patients to this treatment. Mellor *et al.* did not base this conclusion on any 'validated' method of pain scoring, which is a strength (e.g. see the comment relimited sensitivity) as much as it is a weakness. Perhaps (and particularly with the great benefit of hindsight) it would have been preferable to tell all patients 'We know this injection can be unpleasant at first for some people, but there is some evidence that it may provide better pain relief for the endodontic procedure – the really crucial stage – than local anaesthetic alone. Therefore we will track your experience of pain over time to assess whether the advantage later outweighs the earlier disadvantage.' Had they done this, they might have felt less compelled to terminate the study prematurely.

Hargreaves complains that Mellor *et al.* did not report pain outcome figures. This is for two reasons. The study was not able to assess the overall effect on pain in the way that was planned. It would have been inappropriate to present the usual statistical analyses, given that premature termination for unacceptability occurred. Furthermore, the adverse effect, described in some places as 'pain' and elsewhere as 'discomfort', occurred at a time point at which they had not planned to score pain. What is certain is that the conclusion reached by Mellor *et al.* cannot be a consequence of limited sample size. Had a statistical analysis been reported, this could well have failed to demonstrate benefit, for this reason. But Mellor *et al.* reached their conclusion simply because a substantial proportion of patients found the active treatment unacceptable.

The acceptability of injecting any substance could well differ between anatomical sites. Clearly the evidence from the two other endodontic trials referred to by Hargreaves is of some relevance, although it is conceivable that even the injection sites used by Penniston it is quite possible that the treatment may be much better tolerated for orthopaedic sites, or even sites close to the eye, than at intra-oral ones.

Robert G. Newcombe PhD, CStat, FFPH
Professor of Medical Statistics
Consultant Statistician to IEJ
Cardiff University