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Comprehensive review

Evidence for efficacy of acute treatment of episodic tension-type headache: Methodological critique of randomised trials for oral treatments

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ABSTRACT

The International Headache Society (IHS) provides guidance on the conduct of trials for acute treatment of episodic tension-type headache (TTH), a common disorder with considerable disability. Electronic and other searches identified randomised, double-blind trials of oral drugs treating episodic TTH with moderate or severe pain at baseline, or that tested drugs at first pain onset. The aims were to review methods, quality, and outcomes reported (in particular the IHS-recommended primary efficacy parameter pain-free after 2 hours), and to assess efficacy by meta-analysis. We identified 58 reports: 55 from previous reviews and searches, 2 unpublished reports, and 1 clinical trial report with results. We included 40 reports of 55 randomised trials involving 12,143 patients. Reporting quality was generally good, with potential risk of bias from incomplete outcome reporting and small size; the 23 largest trials involved 82% of patients. Few trials reported IHS outcomes. The number needed to treat values for being pain-free at 2 hours compared with placebo were 8.7 (95% confidence interval [CI] 6.2 to 15) for paracetamol 1000 mg, 8.9 (95% CI 5.9 to 18) for ibuprofen 400 mg, and 9.8 (95% CI 5.1 to 146) for ketoprofen 25 mg. Lower (better) number needed to treat values were calculated for outcomes of mild or no pain at 2 hours, and patient global assessment. These were similar to values for these drugs in migraine. No other drugs had evaluable results for these patient-centred outcomes. There was no evidence that any one outcome was better than others. The evidence available for treatment efficacy is small in comparison to the size of the clinical problem.

1. Introduction

Tension-type headache (TTH) was the second most prevalent condition in the 2010 analysis of the global burden of disease [81]. Its prevalence of 21% was higher than that of migraine (15%), the third most prevalent condition. The 2013 International Headache Society (IHS) classification [29] divides TTH into episodic or chronic on the basis of the number of headache days per month. This review is concerned with frequent episodic TTH, defined as at least 10 episodes of headache on 1 to 14 days per month for at least 3 months ($\geqslant$12 and <180 days per year). Infrequent TTH has <1 day of headache per month, and chronic TTH $\geqslant$15 days per month.

Trials for the treatment of acute episodes of TTH are relatively few in number [27,78]. The trials have methodological deficiencies that may lead to bias, and the outcomes used are often complicated and rarely consistent between trials; many test drugs that are not in common use. We therefore undertook a systematic review of clinical trials of oral agents for treating acute attacks of episodic TTH. It had a number of objectives.

1. This study sought to find all the randomised, double-blind trials of oral drug therapy for episodic TTH, and to review the methods used and quality issues that might arise using IHS guidelines for controlled trials of drugs in TTH [2].

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2. This study sought to review outcomes reported in randomised, double-blind trials of treatments for acute episodic TTH, and to establish which report useful patient-centred outcomes. Here a patient-centred outcome is defined as one important to patients, and easily explainable; for example, the percentage of patients pain-free 2 hours after taking a medicine is understandable, important, and recommended as the primary efficacy parameter by the IHS. The pain intensity difference (PID) over 2 hours may demonstrate an analgesic effect, but is not easily explained or understood by professionals or headache sufferers.
3. This study sought to carry out meta-analyses, if possible, to assess the evidence for efficacy of oral analgesic drugs in treating acute episodic TTH using patient-centred outcomes.

2. Methods

All searching, trial selection, and data extraction was done independently by 2 authors and checked by a third.

2.1. Searching

We searched for trials in 5 ways. We obtained copies of all of the studies included in previous systematic reviews (principally [27,78]); performed electronic searches of the literature to January 31, 2014, using PubMed, EMBASE, and Cochrane Central (Appendix 1); searched clinicaltrials.gov for any ongoing trials with results; requested clinical trial reports of unpublished studies in TTH from Reckitt Benckiser; and examined bibliographies of trials and reviews for additional studies.

2.2. Inclusion criteria

Included trials had to be randomised, double-blind comparisons of any active oral therapy with any oral placebo, and/or another active therapy, in adults or children, and with a minimum of 10 patients per treatment arm. Headache pain generally had to be moderate or severe; studies enrolling patients with only mild pain were excluded, as were those in which the occurrence of at least moderate pain could not be demonstrated. The exception was studies deliberately testing drugs at first onset of headache pain.

2.3. Quality assessment

Quality was assessed in 2 ways. Firstly, we used the Oxford Quality Scale, a 5-point scale based on reporting of randomisation, blinding, and withdrawal and dropouts [32]. Secondly, we used a modified risk of bias approach as suggested by the Cochrane Collaboration, using the criteria of appropriateness of method of randomisation, allocation concealment, blinding, dealing with incomplete outcome data, and treatment group size (Appendix 2). Study duration was not included because it is inappropriate for acute treatments, and outcomes were not used because the outcomes reported were the subject of specific study.

2.4. Outcomes in clinical trials

The IHS has provided guidance on clinical trials in TTH [2]. This document specifies what outcomes could be reported in drug trials dealing with the acute treatment of TTH. These are, briefly:

- Patients who are pain-free after 2 hours (recommended as primary efficacy parameter and with presentation of a number needed to treat [NNT])
- Results based on a categorical pain scale, with PID over 2 hours as a possible outcome
- Some measure of disability
- Use of rescue medication
- Global evaluation of the efficacy of the medication
- Adverse events
- Patient preference
- Consistency of effect (in crossover trials)

These suggestions are similar to, if a little different from, the guidance on outcomes for treatment of acute migraine [31]. The differences may reflect the different conditions, or changes in emphasis over time.

A systematic review of patients' views indicated that the evidence we have is that a low pain state, no worse than mild pain, is consistently rated highly by patients in clinical trials when validated against other outcomes, such as reduced depression, improved sleep, better functioning, higher quality of life, and improved ability to work [50]. Migraine patients want pain to be significantly reduced, quickly, without recurrence, and ideally without adverse effects [43]. This suggests that additional patient-centred outcomes of interest in TTH might usefully be:

- Patients who are pain-free after 1 hour
- Patients with mild or no pain after 2 hours
- Patients with mild or no pain after 1 hour

Clearly any trial using periodic measures of headache pain will have these results recorded, but they may not have been reported. These additional outcomes are similar to the reporting of outcomes seen in Cochrane Reviews of acute treatments for migraine [40]; cluster headache, although not in any way comparable with TTH, also uses early outcomes because these headaches usually resolve naturally in about an hour [41]. One-hour outcomes might be particularly important in studies of formulation or route of administration of drugs in which speed of onset was an issue. Longer-duration outcomes are not important for episodic TTH because the headache will resolve spontaneously.

We examined each trial or report for a defined primary outcome matching one specified by the IHS guidance, or our additional outcomes. In addition, each trial or report was examined to see whether each of the 11 outcomes was measured, and whether an appropriate dichotomous outcome was either reported or calculable. If it was available in graphic form, we estimated the result from the graph.

2.5. Efficacy calculations

There was no prior intention to perform a meta-analysis of treatment efficacy because consistently reported outcomes for the same treatment were expected in no more than a few trials. If there were sufficient data (defined as at least 2 trials and 200 patients [48]), we calculated risk ratio and NNT with 95% confidence intervals. Relative benefit or risk was calculated using a fixed effect model [52] with no statistically significant difference between treatments assumed when the 95% confidence intervals included unity. NNT was calculated [7] using the pooled number of observations only when there was a statistically significant difference of relative benefit or risk.

2.6. Terminology

We use the word report to indicate a published or unpublished document that contains information on one or more clinical trials. The word trial is used to indicate a specific clinical trial. A report may have data on one or more trials; it may present data from different trials separately or combine them. Where possible we preferred to use data from individual trials, but in some cases this was not possible and aggregated data were then used if presented.