Comparative clinical effects of hydromorphone and morphine: a meta-analysis

CRD summary
The authors concluded that hydromorphone may have been a slightly more effective pain-killer than morphine, but further studies were needed to confirm this. In view of the limited number and size of the trials, heterogeneity and limited size of the effects, the conclusions may not be sufficiently cautious and it is unclear whether they are reliable.

Authors' objectives
To compare the clinical benefits of hydromorphone with morphine to relieve pain.

Searching
PubMed and EMBASE were searched for studies published between 1970 and June 2009. References of included studies were also searched. Authors were contacted for additional data. Search terms were reported.

Study selection
Studies that evaluated the analgesic and side-effects of hydromorphone compared with morphine were eligible for inclusion. Randomised controlled trials (RCTs) or observational studies were considered. Studies that did not compare hydromorphone with morphine, used only in vitro tests or animal data, or reviews that did not contain original controlled data were excluded.

Patients were treated in different clinical settings for various conditions, such as acute pain (particularly following surgery) and chronic cancer pain. Routes of administration were oral, intravenous or subcutaneous. Some studies used a single dose, whilst a minority used patient-controlled analgesia (PCA), where reported. Dosing varied widely.

Pain outcomes were measured using a 100mm visual analogue scale (VAS) or an 11-point numerical rating scale (NRS).

Two reviewers independently selected studies for inclusion and resolved discrepancies.

Assessment of study quality
Study quality was assessed using the 5 point Jadad scale, which covered randomisation, blinding, description of drop-outs and withdrawals. Allocation concealment was assessed using the criteria by Schulz and Grimes.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data on opioid effects (analgesia and side effects) were extracted to calculate differences in mean between hydromorphone and morphine groups. Pain intensity values were combined if they were reported for different time points.

Two reviewers independently extracted the data and resolved discrepancies.

Methods of synthesis
Standardised mean differences (SMDs) were pooled using a random-effects model. An absolute value of d=0.2 indicated a small effect size, 0.5 a medium one and 0.8 a large one. Heterogeneity was assessed using \( Q \) and \( I^2 \). Outcomes for acute and chronic pain were examined separately in subgroup analyses. Publication bias was assessed using a classic fail-safe \( N \) test. Sensitivity analyses were conducted to test the robustness of the results by removing each study successively.

Results of the review
Eleven controlled trials were included, of which eight examined pain outcomes (1,004 patients), and three investigated side-effects only. Jadad quality scores were between 3 and 5 out of 5 for all trials except one which scored 0.
Patients who received hydromorphone had significantly better analgesia than those who received morphine (d=-0.266, p=0.006, eight trials). Heterogeneity was high (I²=73.6%).

Subgroup analyses showed that there was a significant difference favouring hydromorphone for acute pain treatment (d=-0.228, p=0.012, four trials), but no difference for chronic cancer pain (four trials).

Side effects outcomes were reported, and suggested no significant difference between hydromorphone and morphine.

Sensitivity analyses showed that the overall treatment effect did not substantially change after removal of individual studies.

**Authors' conclusions**
Hydromorphone may have been a slightly more effective pain-killer than morphine, but further studies were needed to confirm this due to heterogeneity and the limited number of studies.

**CRD commentary**
The review question and inclusion criteria were clear. Two bibliographic databases and citations were searched, and authors were contacted for additional data. Appropriate steps were taken to minimise the risk of error and bias during study selection and data extraction. The authors did not report whether similar steps were taken during quality assessment.

Most trials were found to have been of medium to good quality, although only summary scores were reported, which limited the extent to which study quality could be interpreted. Details of the interventions appeared appropriately reported. Reporting of patient characteristics was limited, so the applicability of the conclusions was unclear.

The analyses appeared appropriate. Heterogeneity was high. Some attempts were made to explore potential sources of heterogeneity. The analyses included relatively few studies and the overall result was small (as acknowledged by the authors). Confidence intervals were not reported, which made the interpretation difficult. Sensitivity analyses suggested that the overall results of the analysis were robust.

The conclusions reflected the evidence presented but may not have been sufficiently cautious in view of the limited number and size of the trials, heterogeneity, limited magnitude of treatment effect and robustness of results.

**Implications of the review for practice and research**
**Practice**: The authors stated that the review did not justify a preference for the current use of morphine.

**Research**: The authors stated that additional comparative studies of hydromorphone were needed. More clinical research was needed to assess the pharmacokinetic advantages of hydromorphone and perceived benefits on side-effects. Notably, safety in renal failure or during acute analgesia titration required further investigation.

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