The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review

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CRD summary
This review assessed the effects of opioid analgesics on postoperative delirium and cognitive decline in elderly patients. The authors reported an increased risk of postoperative delirium associated with meperidine, but no apparent differences associated with the mode of drug delivery. Given that studies used different outcome measures and definitions, and lacked statistical power, the authors' findings should be interpreted with caution.

Authors' objectives
To determine the effects of opioid analgesics on post-operative delirium and cognitive decline in elderly patients.

Searching
CINAHL and PubMed were searched from 1966 to 2005; the search terms were reported. In addition, the reference lists of retrieved articles were screened for further studies.

Study selection
Study designs of evaluations included in the review
Comparative studies, including clinical trials and observational studies (i.e. cohort and case-control studies), were eligible for inclusion in the review.

Specific interventions included in the review
Studies comparing different types of opioid analgesics in the post-operative period or modes of delivery (such as intravenous, spinal or epidural) were eligible for inclusion. Studies comparing intramuscular or subcutaneous delivery methods were excluded from the review. The studies included in the review assessed morphine, fentanyl, hydromorphone, tramadol, meperidine, oxycodone and codeine. Intravenous and epidural modes of drug delivery were compared. In some studies drug administration was patient controlled (patient-controlled analgesia).

Participants included in the review
The review question and title suggested that studies including elderly patients who had undergone surgery were eligible for inclusion. However, the authors did not report eligibility criteria for patient age or type of surgery and younger patients were included. The studies included in the review assessed various groups of patients with mean ages ranging from 40 to 82.8 years; 2 studies included patients with mean ages of 51 years or less and did not include mainly elderly patients. Various types of surgery were included: hip, knee, abdominal, and breast surgeries, along with unspecified gynaecological and orthopaedic surgeries. One case-control study compared elderly patients experiencing delirium with those not experiencing delirium after gynaecological or orthopaedic surgery.

Outcomes assessed in the review
To be eligible for inclusion, the studies had to assess postoperative cognitive function or delirium using defined methods. The studies included in the review assessed postoperative cognitive function using a variety of scales and methods: Digit Symbol Substitution, Trail A, Trail B, Profile of Mood States, Mini Mental Status Examination and Short Portable Mental Status Questionnaire. Delirium was assessed using the Abbreviated Mental Test, Confusion Assessment Method, chart review, or by monitoring clinical signs such as disorientation, hallucination and inappropriate behaviour. Two studies used the American Psychiatric Association's DSM III criteria to define delirium. Some studies also assessed pain using methods such as a visual analogue scale or a verbal rating scale.

How were decisions on the relevance of primary studies made?
One reviewer screened all of the retrieved study abstracts for inclusion or exclusion. A second reviewer validated studies to be included in the review and also checked those excluded studies where uncertainty arose.
Assessment of study quality
The validity of randomised controlled trials (RCTs) was assessed according to randomisation, blinding, and withdrawals and drop-outs. The studies were each awarded a score of between 1 and 5; details of the scoring system were reported. The authors did not state how many reviewers were involved in this process.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Details of any criteria or definitions used to define delirium or postoperative cognitive function were extracted. Where possible, the power of the studies was extracted or calculated by comparing the proportion of the group of patients with the higher rate of delirium against a hypothesised decrease of 10%, given the sample sizes reported by the study. Outcome data were extracted as reported in the original studies, with percentages or odds ratios (with 95% confidence intervals, CIs) reported, where available, for incidences of delirium.

Methods of synthesis
How were the studies combined?
The studies were grouped according to whether they compared different types of drugs or different modes of administration. Each study was then briefly described in the tables and in a short narrative.

How were differences between studies investigated?
Some differences between the studies were evident from the data tables, whilst others were described within the text of the review.

Results of the review
Ten studies (1,269 participants) were included in the review: seven RCTs (391 participants), one prospective cohort study (541 participants), one retrospective cohort study (92 participants) and one case-control study (245 participants).

Studies comparing different opioid analgesics (three RCTs, one prospective cohort, one retrospective cohort and one case-control study): Most of the studies were limited by small sample sizes. All three RCTs found no significant differences in cognitive function or delirium when comparing patient-controlled analgesia morphine with patient-controlled analgesia fentanyl (quality score 2), patient-controlled analgesia hydromorphone (quality score 4) and patient-controlled analgesia tramadol (quality score 5). The studies comparing morphine with hydromorphone and tramadol did not include mainly elderly participants. All three observational studies found significantly poorer delirium and/or cognitive outcomes for the meperidine groups when comparing meperidine with morphine (retrospective cohort study), morphine and other opiates (prospective cohort), and morphine, fentanyl, oxycodone, and codeine (case-control study).

Studies comparing different modes of delivery (four RCTs and one case-control study): Many studies were limited by small sample sizes and different definitions of postoperative cognitive function and delirium. All five studies assessed predominantly elderly patients. All four RCTs found no significant differences between intravenous and epidural drug delivery with respect to delirium (two trials, both with quality scores of 3) and postoperative cognitive function (two trials, quality scores of 4 and 2). The case-control study found poorer delirium outcomes for patients receiving epidural analgesia. However, 85% of patients in the epidural group received meperidine and no multivariate analysis was performed to take this confounding variable into account.

Authors' conclusions
Evidence suggested an increased risk of post-operative delirium associated with the use of meperidine in elderly surgical patients. There was no evidence of a significant decline in postoperative cognitive function or an increased incidence of delirium in patients receiving other opioids such as morphine, fentanyl or hydromorphone. The mode of drug delivery (intravenous or epidural) did not appear to influence cognitive function. However, further research is required to confirm these findings.

CRD commentary
This review was based on clear inclusion criteria that were defined for the intervention, study design and outcomes,
but the types of participants eligible for inclusion were not defined. Although the title of the review and the research question implied that the review was looking at the effects of opioids in elderly postoperative patients, two of the included studies did not assess mainly elderly participants. The limited literature searches may be subject to publication bias, as no specific attempts were made to locate unpublished data. It was unclear whether language restrictions were imposed. It was difficult to assess whether appropriate steps were taken to reduce the risk of bias and error when assessing the validity of the studies and extracting the study data.

The validity of the RCTs was assessed using limited, but appropriate criteria, but no criteria were reported for an assessment of the other study designs. Details of the individual studies were provided. Given the differences between the studies, a narrative summary of the findings seemed appropriate. However, many of the studies lacked statistical power and comparisons were difficult given the use of different outcome measures and definitions.

Therefore, the review's conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors stated that meperidine appeared to be the only opioid analgesic whose use should be clearly avoided in elderly patients.

**Research:** The authors stated that further research was required to confirm the review's findings. Future studies should use standardised measures and definitions of cognitive function and delirium, and use neuropsychological tests to target sensitive domains. Studies should ensure that they recruit sufficient numbers of participants to discern meaningful differences in outcomes, and also assess post-operative pain.

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