Ketamine and postoperative pain: a quantitative systematic review of randomised trials

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CRD summary
This review assessed the efficacy and safety of ketamine for the control of post-operative pain. The authors concluded that the role of ketamine in peri-operative analgesia remains unclear. The authors acknowledged that the evidence was weak in some areas. However, their conclusions appear suitably cautious and the recommendations for further research seem reasonable.

Authors’ objectives
To assess the benefits and harms of ketamine for the control of post-operative pain.

Searching
MEDLINE, EMBASE, CINAHL, Biosis Previews, IndMED and the Cochrane Controlled Trials Register were searched to November 2003 using the reported search terms. The bibliographies of retrieved reports and reviews were screened. The manufacturers of ketamine were contacted for additional reports including unpublished studies. The authors of the original papers were contacted for translations or for additional information. Abstracts were not included in the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 10 patients per treatment group were eligible for inclusion.

Specific interventions included in the review
Studies that compared ketamine for post-operative pain management with an inactive control (placebo or no treatment) were eligible for inclusion. Studies of premedication, chronic pain or emergency medicine were excluded. The included studies used a wide variety of different ketamine regimens and routes of administration (intravenous, intramuscular, subcutaneous, intra-articular, caudal, epidural, transdermal, peripheral and patient-controlled analgesic devices; full details were reported). Most of the studies used racemic ketamine; four used the S(+) ketamine isomer. The review classified ketamine regimens as prophylactic (at induction of anaesthesia and during or immediately after surgery) or therapeutic (post-operatively to patients complaining of pain).

Participants included in the review
Although inclusion criteria for the participants were not specified, it was clear that studies of patients undergoing surgery were eligible for inclusion in the review. The included studies were in adults and children undergoing a wide variety of different types of surgery (details were reported).

Outcomes assessed in the review
Studies that reported measures of post-operative pain (pain intensity, time to first request for analgesia, cumulative post-operative morphine consumption and morphine-related adverse effects) or ketamine-related adverse effects were eligible for inclusion.

How were decisions on the relevance of primary studies made?
One reviewer screened abstracts and excluded articles that did not meet the inclusion criteria.

Assessment of study quality
Validity was assessed and scored using a modified 7-point, 4-item Oxford scale which considered the reporting and adequacy of randomisation, allocation concealment, double-blinding and description of drop-outs. Two reviewers independently assessed validity and resolved any disagreements through discussion.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Reported ketamine regimens were standardised to mg/kg body weight; body weight was assumed to be 70 kg where it was not reported.

For each study, relative risks (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous data and mean treatment differences with 95% CIs for continuous outcomes. Within-study data were combined where there was no difference between ketamine given before or after surgery. The authors of the primary studies were contacted for missing data; where data were not obtained, the data were extracted from graphs.

Methods of synthesis
How were the studies combined?
Only clinically homogeneous studies were combined statistically; a fixed-effect meta-analysis was used. The pooled weighted mean difference and 95% CI were calculated for continuous data and the pooled RR and 95% CI for dichotomous data, with Peto odds ratios (ORs) being used to pool rare outcomes. Studies combined in a narrative were grouped by ketamine regimen and type of participant. Pooled ORs with 95% CIs and numbers-needed-to-harm (NNH) were calculated for adverse effects.

How were differences between studies investigated?
Differences between the studies were examined graphically using forest plots and L'Abbe plots.

The impact of the dose of ketamine on efficacy and occurrence of adverse events was assessed; the impact of premedication with benzodiazepine and patient's vigilance at the time of drug administration on hallucinations and on the occurrence of adverse events was also examined.

Results of the review
Fifty-three RCTs (n=2,721) were included.

The median modified Oxford score for quality was 4 out of a possible 7 (range: 2 to 6).

Efficacy.

Pain intensity (10 RCTs): there was a statistically significant reduction in pain intensity at rest with ketamine compared with control at 6 hours (WMD -0.89 cm, 95% CI: -1.13, -0.65), 12 hours (WMD -0.42 cm, 95% CI: -0.72, -0.11), 24 hours (WMD -0.35 cm, 95% CI: -0.60, -0.09) and 48 hours (WMD -0.27 cm, 95% CI: -0.60, -0.09). There was no evidence of a relationship between the dose of ketamine and its analgesic efficacy.

Cumulative morphine consumption at 24 hours (5 RCTs): there was a statistically significant reduction in cumulative morphine consumption at 24 hours with ketamine compared with control (WMD -15.7 mg; 95% CI: -20.9, -10.5).

Opioid-related adverse effects (9 RCTs): there were no statistically significant differences between ketamine and control for any of the specified opioid-related adverse effects (nausea, vomiting, nausea or vomiting, pruritus, drowsiness or urinary retention).

Time to first request for analgesia (7 RCTs): the mean reduction in time to first request for analgesia was 15.7 minutes (95% CI: 12.5, 18.9) with ketamine compared with control.

Efficacy results for other ketamine regimens were also reported.

Safety.

Hallucinations (30 RCTs): there was a statistically significantly increased risk of hallucinations with ketamine (with or without benzodiazepines) in awake or sedated patients compared with controls: 7.4% versus 3.7%. The OR was 2.32
The risk of hallucinations with ketamine (regardless of use or not of benzodiazepines) in patients undergoing general anaesthesia was low: 0.8% versus 0.4%. The OR was 1.49 (95% CI: 0.18, 12.6) and the NNH was 286.

**Authors' conclusions**
The role of ketamine in peri-operative analgesia remains unclear. Recommendations for further research were reported.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise publication and language bias. Only one reviewer selected studies and this lack of duplication might have led to selection bias and missed studies. Methods were used to minimise reviewer errors and bias in the assessment of validity, but it was unclear whether similar steps were taken during the data extraction. Validity was assessed using a defined checklist, although only the composite score was presented; this makes it difficult for the reader to judge the validity of the studies for themselves.

The studies were appropriately grouped and only clinically homogeneous studies were pooled using meta-analysis. Meta-analysis graphs allowed an assessment of differences in the results. The authors acknowledged that the evidence was weak in some areas, owing to a lack of high-quality RCTs. However, their overall conclusions appear suitably cautious and the recommendations for further research seem reasonable.

**Implications of the review for practice and research**
**Practice:** The authors stated that there should be an assessment of the anticipated risks and benefits before giving ketamine to patients who are not anaesthetised. If ketamine is given, the patient should be informed about the risks and should be carefully monitored.

**Research:** The authors stated that future studies could assess higher doses of ketamine in anaesthetised patients undergoing major or painful procedures, and use long-term follow-up to assess the effects of peri-operative ketamine on chronic pain. They also stated that future studies should be adequately powered and should evaluate the effects of ketamine on clinically relevant measures of analgesic efficacy and adverse effects. In addition, the use of ketamine in morphine-resistant pain should be examined and adverse drug reactions should be verified by a reduction in opioid-related adverse effects.

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.