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## Perioperative intravenous ketamine for acute postoperative pain in adults.

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### Abstract

**BACKGROUND:** Inadequate pain management after surgery increases the risk of postoperative complications and may predispose for chronic postsurgical pain. Perioperative ketamine may enhance conventional analgesics in the acute postoperative setting.

**OBJECTIVES:** To evaluate the efficacy and safety of perioperative intravenous ketamine in adult patients when used for the treatment or prevention of acute pain following general anaesthesia.

**SEARCH METHODS:** We searched CENTRAL, MEDLINE and Embase to July 2018 and three trials registers (metaRegister of controlled trials, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)) together with reference checking, citation searching and contact with study authors to identify additional studies.

**SELECTION CRITERIA:** We sought randomised, double-blind, controlled trials of adults undergoing surgery under general anaesthesia and being treated with perioperative intravenous ketamine. Studies compared ketamine with placebo, or compared ketamine plus a basic analgesic, such as morphine or non-steroidal anti-inflammatory drug (NSAID), with a basic analgesic alone.

**DATA COLLECTION AND ANALYSIS:** Two review authors searched for studies, extracted efficacy and adverse event data, examined issues of study quality and potential bias, and performed analyses. Primary outcomes were opioid consumption and pain intensity at rest and during movement at 24 and 48 hours postoperatively. Secondary outcomes were time to first analgesic request, assessment of postoperative hyperalgesia, central nervous

system (CNS) adverse effects, and postoperative nausea and vomiting. We assessed the evidence using GRADE and created a 'Summary of findings' table.

**MAIN RESULTS:** We included 130 studies with 8341 participants. Ketamine was given to 4588 participants and 3753 participants served as controls. Types of surgery included ear, nose or throat surgery, wisdom tooth extraction, thoracotomy, lumbar fusion surgery, microdiscectomy, hip joint replacement surgery, knee joint replacement surgery, anterior cruciate ligament repair, knee arthroscopy, mastectomy, haemorrhoidectomy, abdominal surgery, radical prostatectomy, thyroid surgery, elective caesarean section, and laparoscopic surgery. Racemic ketamine bolus doses were predominantly 0.25 mg to 1 mg, and infusions 2 to 5 µg/kg/minute; 10 studies used only S-ketamine and one only R-ketamine. Risk of bias was generally low or uncertain, except for study size; most had fewer than 50 participants per treatment arm, resulting in high heterogeneity, as expected, for most analyses. We did not stratify the main analysis by type of surgery or any other factor, such as dose or timing of ketamine administration, and used a non-stratified analysis. Perioperative intravenous ketamine reduced postoperative opioid consumption over 24 hours by 8 mg morphine equivalents (95% CI 6 to 9; 19% from 42 mg consumed by participants given placebo, moderate-quality evidence; 65 studies, 4004 participants). Over 48 hours, opioid consumption was 13 mg lower (95% CI 10 to 15; 19% from 67 mg with placebo, moderate-quality evidence; 37 studies, 2449 participants). Perioperative intravenous ketamine reduced pain at rest at 24 hours by 5/100 mm on a visual analogue scale (95% CI 4 to 7; 19% lower from 26/100 mm with placebo, high-quality evidence; 82 studies, 5004 participants), and at 48 hours by 5/100 mm (95% CI 3 to 7; 22% lower from 23/100 mm, high-quality evidence; 49 studies, 2962 participants). Pain during movement was reduced at 24 hours (6/100 mm, 14% lower from 42/100 mm, moderate-quality evidence; 29 studies, 1806 participants), and 48 hours (6/100 mm, 16% lower from 37 mm, low-quality evidence; 23 studies, 1353 participants). Results for primary outcomes were consistent when analysed by pain at rest or on movement, operation type, and timing of administration, or sensitivity to study size and pain intensity. No analysis by dose was possible. There was no difference when nitrous oxide was used. We downgraded the quality of the evidence once if numbers of participants were large but small-study effects were present, or twice if numbers were small and small-study effects likely but testing not possible. Ketamine increased the time for the first postoperative analgesic request by 54 minutes (95% CI 37 to 71 minutes), from a mean of 39 minutes with placebo (moderate-quality evidence; 31 studies, 1678 participants). Ketamine reduced the area of postoperative hyperalgesia by 7 cm<sup>2</sup> (95% CI -11.9 to -2.2), compared with placebo (very low-quality evidence; 7 studies 333 participants). We downgraded the quality of evidence

because of small-study effects or because the number of participants was below 400. CNS adverse events occurred in 52 studies, while 53 studies reported of absence of CNS adverse events. Overall, 187/3614 (5%) participants receiving ketamine and 122/2924 (4%) receiving control treatment experienced an adverse event (RR 1.2, 95% CI 0.95 to 1.4; high-quality evidence; 105 studies, 6538 participants). Ketamine reduced postoperative nausea and vomiting from 27% with placebo to 23% with ketamine (RR 0.88, 95% CI 0.81 to 0.96; the number needed to treat to prevent one episode of postoperative nausea and vomiting with perioperative intravenous ketamine administration was 24 (95% CI 16 to 54; high-quality evidence; 95 studies, 5965 participants).

**AUTHORS' CONCLUSIONS:** Perioperative intravenous ketamine probably reduces postoperative analgesic consumption and pain intensity. Results were consistent in different operation types or timing of ketamine administration, with larger and smaller studies, and by higher and lower pain intensity. CNS adverse events were little different with ketamine or control. Perioperative intravenous ketamine probably reduces postoperative nausea and vomiting by a small extent, of arguable clinical relevance.

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