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(Abstract)

Contents

Systematic Review of Neuropsychiatric Adverse Effects of Ketamine Compared to Other Anesthetic Regimens for Induction or Maintenance of General Anesthesia

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Introduction: Ketamine has been used since the 1960's and was initially developed to create a shorter-acting version of phencyclidine with reduced emergence delirium.[1] Despite favourable cardiorespiratory stability, alternative intravenous anesthetics are often preferred for general anesthesia given the notion that ketamine causes more neuropsychiatric adverse effects.[1] This review aimed to answer the question "What is the difference in incidence rates of neuropsychiatric adverse effects between ketamine and non-ketamine anesthetic regimens for patients undergoing general anesthesia?"

Methods: Ethics approval was not applicable because the study did not involve human or animal research. We independently searched MEDLINE® (1946 to April 2020), EMbase (1974 to April 2020), CINAHL® (1982 to April 2020), and PsycINFO (1597 to April 2020) databases. We included studies if they were clinical trials involving human participants of any ages, undergoing procedures requiring general anesthesia; contained a group receiving ketamine for induction or maintenance of general anesthesia and a group not receiving ketamine; and quantitatively documented neuropsychiatric effects. We excluded studies if ketamine was used: only as an analgesic; only postoperatively; for non-operative care or procedural sedation; or when English full text was unavailable. We assessed the validity of each study using the Centre for Evidence-Based Medicine critical appraisal worksheets for randomized controlled trials. We recorded neuropsychiatric adverse events of each study and calculated the risk differences where appropriate.

Results: From the 722 studies screened, we included 31 in the review. The study populations included pediatric and adult participants. Ketamine doses ranged from 0.3 to 3 $mg \cdot kg^{-1}$ intravenously for induction with some studies also using infusions and boluses as needed for maintenance. Premedication regimens used in the studies included benzodiazepines, anticholinergics, antipsychotics, opioids, and no premedication.

The primary outcomes were unpleasant dreams, agitation, hallucinations, and delirium. Fourteen studies reported unpleasant dreams with three reporting statistically significant risk differences (RD), suggesting ketamine groups had more unpleasant dreams: 6% (95% confidence interval [CI] 1-16%),[2] 23% (95% CI 3-38%),[3] and 36% (95% CI 22-50%).[4] All three studies involved adult women undergoing termination of pregnancy or cesarean section under general anesthetic with a variety of premedication and adjuvant anesthetics. Five studies reported agitation in children undergoing various procedures with one study reporting more agitation in the non-ketamine group (RD 26%; 95% CI 5 - 44%) than in the ketamine group.[5] Four studies reported delirium; none of these studies found statistically significant differences between groups. Six studies included hallucination as an outcome; none found any events in any study group.

Discussion: Overall, there is limited evidence in the published literature to suggest that ketamine has increased rates of neuropsychiatric adverse effects compared to non-ketamine general anesthetic regimens. Limitations of this review include the lack of patient level data and an inability pool incidence rates given significant heterogeneity between studies.

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