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Plasma concentration associated with the analgesic efficacy of intravenous ketamine in postoperative pain: Systematic review and Domino simulation of randomized clinical trials

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REVIEW TITLE AND BASIC DETAILS

Review title
Plasma concentration associated with the analgesic efficacy of intravenous ketamine in postoperative pain: Systematic review and Domino simulation of randomized clinical trials

Condition or domain being studied
General Anesthesia; Postoperative Pain; Ketamine; Surgery; Placebo; Opioids; Side effects; Analgesics

Because of opioid shortage , abuse or addiction, and their sides effects, multimodal analgesia is recommended particularly opioid free anesthesia or analgesia. Severals RCTs studies have demonstrated that ketamine is an excellent adjunct to opioid consumption and reduce the amount of opioids or other analgesic needed. There are a call for opioid reduction but the promotion multimodal analgesia. ketamine function by blocking the NMDA receptors involved in nociceptive and inflammatory pain transmission particularly in surgery. Studies suggested that low dose of ketamine (<1 mg/kg intravenous ou ≤ 20 µg/kg per min continuous) improve post operative pain control. Some studies reported that ketamine is effective for POP control but other did not reported. Among studies that reported POP control , the dose, the route, the time and period of administration are variables form study to another. Then it is not clear about the intervention plan that guarantees the effectiveness of ketamine. Given the multitude of possible intervention regimens (dose, duration, and time of administration) that are difficult to test, it is logical to believe that the efficacy of ketamine is related to its plasma concentration.

Rationale for the review

Postoperative pain (POP) is present in half of patients who undergo surgery. Poorly managed, POP can lead to complications [1] influences patient satisfaction and cost [2, 3]. POP is treated with multimodal analgesia, including opioids [4, 5] [6], which may increase morbidity [7] [8]. Multimodal analgesia uses local and systemic analgesics, including ketamine. Ketamine is a non-competitive antagonist of N-methyl-D-aspartate receptors and its antagonism is responsible of analgesic effect [9][10] and morphine sparing [9]. Analgesic and anti-hyperalgesic properties focus attention in opioid-free anesthesia/analgesia [11][12]. Some studies have reported analgesic efficacy of ketamine [13][14][15]. Some RCT , review [15,16] or meta-analyses [13] report that ketamine reduce POP, while others have not observed efficacy or morphine sparing [13]. Studies find heterogeneity in practices and outcomes [14, 17]. Some guidelines recommend routes [18] or doses [19] or time or both [20] but they recognized the need for further investigation for effective interventional plan [18]. There is no consensus on methods, doses, and routes of administration of ketamine that have proved POP control. Thus, the variability in RCT results are related to diversity of practices and maybe more by related to difference in plasma concentration of ketamine. No RCT have explored the relationship between POP control and ketamine plasma concentration. This review aim to determine the effective plasma concentration associated to POP control using in silico study (simulation, modeling, optimization) of ketamine based on published RCTs. The expected results of this study will be the subject of a RCT to verify the hypothesis.

Review objectives

The purpose of this review is to compile study data for RCTs compile data from RCTs reporting analgesic efficacy of intravenous ketamine during general anesthesia *with reduction of postoperative pain score and opioid consumption compared with placebo.*

The compiled data will be analyzed in silico to determine whether RCTs in which ketamine has been shown to be effective correspond to a significantly higher plasma concentration than those in which it has not been shown to be effective.

Specific objectives are to determine average plasma concentration of ketamine associated with POP control, to determine mass dose of ketamine associated with the effective plasma concentration and to compare tolerability of ketamine according to plasma concentration level

Keywords

Surgery; Ketamine; Randomized controlled trials; Postoperative pain; Analgesia; Systematic review

Country

Burkina Faso; France

ELIGIBILITY CRITERIA

Population

Included

1° Type of study : Randomized clinical trials (RCTs) , reviews of RCTs, meta-analyses of RCTs

2° Conditions of study:

- involving patients 18 years old or above underwent surgery under general anesthesia ;

- with placebo as comparator

- registered in a clinical trial database or review database

- that reported acute postoperative pain score with at least 3 days follow-up after surgery

- published between 1990 and 2024 in French or English

Excluded
- RCTs for which the full text is not available

- Crossover or open-label RCTs

- RCTs on acute non-surgical pain

- RCTs in which ketamine doses are not specified

- RCTs using multiple comparators or other than placebo

- RCTs on chronic post operative pain

Intervention(s) or exposure(s)

Included
Ketamine; Placebo

- Patients received general anesthesia for surgery with or without regional anesthesia.

- Intervention consist of ketamine alone administered intravenously during general anaesthesia or perioperatively for the treatment or prevention of acute postoperative pain in adult patients. The administration is a bolus or infusion at induction period , incision, intra operatively, or postoperatively. Only ketamine low dose is considered.

Use of regional anesthesia in the two group

Excluded
- The administration of ketamine by other routes than IV

- The use of ketamine in association to gabapentin or other analgesic adjuvants

- The use of RA in one group

- The of kétamine in high dose

- Chronic use of kétamine

Comparator(s) or control(s)

Included
PICO tags selected: Placebo

The comparator is only a placebo blinded , at the same dose or volume than ketamine.

Excluded
The use of other comparator than placebo ou association of placebo to other comparator.

Study design
Only randomized study types will be included.

Included
We will include randomised studies, review of randomised studies or meta analyze of randomised studies.

Excluded
We will exclude open label trial, cross over trial, non randomized trial.

Context
Although mechanisms of action of ketamine are better understood, analgesic and antihyperalgesic efficacy has been proven, there is no standard practice that guarantees its efficacy and tolerance. A systematic review of perioperative intravenous ketamine incorporating more than 8,000 patients [13], demonstrated efficacy, but only true for some surgeries. Meyer-Friebem et al [21] conducted a meta-analysis on the perioperative ketamine for the management of postoperative pain in opioid users. They did not report immediate analgesic efficacy, but opioid savings, a low rate of sedation, and opioid-induced antihyperalgesia. However, due to clinical heterogeneity, the authors suggest further studies [14], [21], [23]. Regimens aimed at analgesia, prevention, morphine sparing, or antihyperalgesia [22] have been described, but these three regimens all have different dosages with different results. The antihyperalgesic effect is the effect related to the potentiation of the effects of opioids by ketamine. The effects of ketamine are concentration-dependent. The plasma concentration of ketamine K[c] associated with an analgesic effect is between 100 and 500 ng/ml, and it has been proven that the analgesic effect persists as long as concentrations remain above 100–150 ng/ml [22], with an ideal concentration between 100 and 200 ng/ml [23]. Between 20 and 100 ng/ml, ketamine no longer has an analgesic effect on its own but potentiates opioids, which is its anti-hyperalgesic effect [24]. Based on a comparison between clinical studies with proven efficacy and those in which ketamine is ineffective, an in silico study will determine whether efficacy is indeed linked to higher plasma concentrations.

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO
31 July 2025

Review timeline
Start date: 30 August 2025. End date: 30 June 2026.

Date of registration in PROSPERO
31 October 2025

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol
A full protocol has been written and uploaded to PROSPERO. The protocol will be made available after the review is completed.

SEARCHING AND SCREENING

Search for unpublished studies

Only published studies will be sought.

Main bibliographic databases that will be searched
The main databases to be searched are *CENTRAL - Cochrane Central Register of Controlled Trials*, *CLIB - The Cochrane Library*, *Embase - Embase via Ovid*, *MEDLINE*, *PubMed* and *Scopus*.

Search language restrictions
The review will only include studies published in English and French.

Search date restrictions
Databases will be searched for articles published from 31 December 1990 and before by 31 December 2024.

Other methods of identifying studies
Other studies will be identified by: *contacting authors or experts*, *looking through all the articles that cite the papers included in the review ("snowballing")*, *reference list checking*, *searching conference proceedings*, *searching dissertation and thesis databases* and *searching trial or study registers*.

Additional information about identifying studies
No

Link to search strategy
A full search strategy is available in the full protocol as described in the *Availability of full protocol* section

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening
The sources of information are electronic databases, email contacts of authors of published studies; clinical trial registers and registers of reviews or meta-analyses. Databases are MedLine (PubMed), Scopus , Cochrane Library, Web of Science, Clinical trials and PROSPERO. The research for articles will use the keywords " Medical Subject Headings (MeSH): MeSH "acute pain", "surgery", "postoperative", "acute pain", " surgery " "post operative ", and associated with the keyword " ketamine " "S-ketamine, Esketamine S- (+)- ketamine". The final search equation will be: MeSH "acute pain" AND MeSH "post operative " AND " ketamine " or "acute pain" and "postoperative" and "ketamine".

The first step is the search in the reference lists of the included articles (meta-analyses, clinical trials), the second step will be the performance of citation tracking and the third step will concern the articles "related to" or "similar" to the selected articles. Each method will be applied by 2 independent reviewers. Two authors (GM and ML) will read and select the relevant studies independently and, in case of disagreement, a third author (CC) or even a fourth author (MO) will decide. The first selection of articles will be based on the title, abstract and their bibliography. The second selection will be based on the entire article with justification for each exclusion. Duplicates will be removed using PowerQuieri and an Excel will be used to classify studies. We included the PRISMA diagram [25] , according to Cochrane Handbook for Systematic Reviews of Interventions [30] .

DATA COLLECTION PROCESS

Data extraction from published articles and reports
Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will be asked to provide any required data not available in published reports.

Study risk of bias or quality assessment
Risk of bias will be assessed using: *Cochrane RoB-2*

Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment
We will identify sources of missing data (unpublished, outcome, results not reported). ROB-ME tool will be used for meta-analyses. A sensitivity analyse will explore the impact of missing data on the synthesis. We will consider reasons for missing data to assess the impact on synthesis and acknowledge limitations.

Certainty assessment
Studies will be classified in term of level of evidence according to the Oxford Centre for Evidence Based Medicine [37] by three evaluators.

OUTCOMES TO BE ANALYSED

Main outcomes
1° Efficacy of ketamine in the RCTs

The efficacy is define as a discount a difference in pain score (percentage) or a discount for a difference in raw pain score on numerical scale (0 to 10 cm);

2° Mean plasma concentration and the area under the plasma concentration curve in group with efficacy versus group without efficacy

- It will be a simulated concentration using pharmacokinetic model (K

Additional outcomes
Additional outcomes will be :

-Ketamine adverses effects

-Reduction in postoperative total opioid consumption in percentage ou absolute value

-Reduction of other painkillers consumption

- Patient satisfaction

PLANNED DATA SYNTHESIS

Strategy for data synthesis

Data synthesis will done using PRISMA guideline 2025. The data will be aggregated. The dosages for each study will be carefully recorded and then used to calculate the theoretical plasma concentrations of ketamine generated by administration in each study. The average concentrations will then be calculated for studies considered effective and for those considered ineffective. Plasmatic concentrations will be calculated using the Domino pharmacokinetic model. Finally, the two areas under the concentration curve in each group will be compared.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work		
Formal searching/study identification		
Screening search results against inclusion criteria		
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Review status

The review is currently planned or ongoing.

Publication of review results

Results of the review will not be published.

The data will be aggregated and the work is part of a thesis (student) and therefore will not be published on the website.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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Funding source
Review has no specific/external funding but is supported by guarantor/review team (non-commercial) institutions.

Additional information about funding
Personal funding

Peer review
Professor Patrice Forget, anesthesiologist at University of Aberdeen review the protocol.

Dr Cheurfa Cherifa , anesthesiologist, APHP Paris , France review the protocol.

ADDITIONAL INFORMATION

Additional information
This review enter in the process of PhD study in pharmacology.

Review conflict of interest
Declared individual interests are recorded under team member details.. No additional interests are recorded for this review.

Medical Subject Headings
Administration, Intravenous; Analgesia; Analgesics; Anesthesia, Conduction; Anesthesia, General; Humans; Ketamine; Pain, Postoperative; Randomized Controlled Trials as Topic

SIMILAR REVIEWS

Check for similar records already in PROSPERO
PROSPERO identified a number of existing PROSPERO records that were similar to this one (last check made on 24 July 2025). These are shown below along with the reasons given by that the review team for the reviews being different and/or proceeding.

- Perioperative ketamine for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of randomised controlled trials [published 13 February 2021] [CRD42021227332]. The review was judged **not to be similar**
- Perioperative intravenous ketamine for acute postoperative pain in adults [Cochrane Protocol] [published 3 August 2016] [CRD42016044129]. The review was judged **not to be similar**
- Ketamine infusion in chronic pain patients: a meta-analysis of randomized controlled trials [published 28 August 2017] [CRD42017075521]. The review was judged **not to be similar**

- Comparative Efficacy of Ketamine Versus Midazolam for Suicidality: A Meta-Analysis of Randomized Controlled Trials [published 22 July 2025] [CRD420251110292]. The review was judged **not to be similar**
- Efficacy and Safety of Ketamine Versus Morphine in Prehospital Analgesia for Traumatic Pain : A Systematic Review and Meta-analysis of Randomized Controlled Trial. [published 24 July 2024] [CRD42024568884]. The review was judged **not to be similar**
- A systematic review and meta-analysis on ketamine uses and the risk of postoperative delirium [published 9 April 2025] [CRD420251024716]. The review was judged **not to be similar**
- The effect of intravenous ketamine for patients with acute pain in emergency setting [published 15 July 2015] [CRD42015024337]. The review was judged **not to be similar**
- Efficacy and safety of Ketamine for treatment of cancer pain in adult patients A systematic review and meta-analysis. [published 23 November 2022] [CRD42022375354]. The review was judged **not to be similar**
- Low-dose Intravenous Ketamine and Postoperative Pain Management: A System Review and Meta-analysis [published 22 February 2023] [CRD42023397736]. The review was judged **not to be similar**
- The Use of Ketamine for Treatment of Neuropathic pain in Cancer Patients: A Systematic Review of Randomized Controlled Trials [published 21 April 2025] [CRD420251035730]. The review was judged **not to be similar**
- The Therapeutic Efficacy of Ayahuasca, Ketamine, and MDMA for Treating Depression and PTSD: A Meta-Analysis [published 19 February 2021] [CRD42021232149]. The review was judged **not to be similar**
- Effect of perioperative application of ketamine on postoperative depression : a systematic review and meta-analysis with trial sequential analysis [published 12 June 2023] [CRD42023431566]. The review was judged **not to be similar**
- Ketamine versus Opioid Analgesics for Acute Trauma Pain in Adults: A Systematic Review and Meta-Analysis of RCTs in Prehospital and Emergency Department Settings [published 8 May 2025] [CRD420251036351]. The review was judged **not to be similar**
- Double Relief: Systematic Review and Meta-analysis on the Use of Low-Dose Ketamine Combined with Morphine for Acute Trauma Pain Management [published 11 July 2025] [CRD420251101444]. The review was judged **not to be similar**
- Comparative efficacy and safety of intranasal versus intravenous ketamine in the treatment of treatment-resistant depression in adults: A systematic review [published 11 April 2025] [CRD420251030702]. The review was judged **not to be similar**
- Perioperative administration of different doses of ketamine or esketamine on postoperative depression and pain: A systematic review and network meta-analysis [published 29 January 2025] [CRD42025640026]. The review was judged **not to be similar**
- Perioperative Ketamine for Analgesia in spinal surgery: : a proposed systematic review and meta-analysis [published 25 March 2021] [CRD42021238943]. The review was judged **not to be similar**
- The effect of intravenous S-ketamine on postoperative depression under general anesthesia: A systematic review and meta-analysis of randomized controlled trials [published 28 March 2024] [CRD42024525202]. The review was judged **not to be similar**
- The safety of ketamine use in children [published 30 September 2021] [CRD42021281972]. The review was judged **not to be similar**

- Intraoperative intravenous ketamine for postoperative analgesia [published 20 October 2014] [CRD42014013845]. The review was judged **not to be similar**

PROSPERO version history

- Version 1.0, published 31 Oct 2025

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