



Systematic review

Intra- and postoperative intravenous ketamine does not prevent chronic pain: A systematic review and meta-analysis[☆]



Elena Klatt^a, Thomas Zumbunn^b, Oliver Bandschapp^a,
Thierry Girard^a, Wilhelm Ruppen^{a,*}

^a Department for Anaesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University of Basel Hospital, CH-4031 Basel, Switzerland

^b Clinical Trial Unit, University of Basel Hospital, CH-4031 Basel, Switzerland

HIGHLIGHTS

- The perioperative use of ketamine does not prevent postoperative chronic pain.
- One month after surgery there was a marginal reduction of postoperative chronic pain using ketamine.
- Regional anaesthesia combined with ketamine might have a preventive effect.

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ABSTRACT

Background and aims: The development of postoperative chronic pain (POCP) after surgery is a major problem with a considerable socioeconomic impact. It is defined as pain lasting more than the usual healing, often more than 2–6 months. Recent systematic reviews and meta-analyses demonstrate that the *N*-methyl-*D*-aspartate-receptor antagonist ketamine given peri- and intraoperatively can reduce immediate postoperative pain, especially if severe postoperative pain is expected and regional anaesthesia techniques are impossible. However, the results concerning the role of ketamine in preventing chronic postoperative pain are conflicting. The aim of this study was to perform a systematic review and a pooled analysis to determine if peri- and intraoperative ketamine can reduce the incidence of chronic postoperative pain.

Methods: Electronic searches of PubMed, EMBASE and Cochrane including data until September 2013 were conducted. Subsequently, the titles and abstracts were read, and reference lists of reviews and retrieved studies were reviewed for additional studies. Where necessary, authors were contacted to obtain raw data for statistical analysis. Papers reporting on ketamine used in the intra- and postoperative setting with pain measured at least 4 weeks after surgery were identified. For meta-analysis of pain after 1, 3, 6 and 12 months, the results were summarised in a forest plot, indicating the number of patients with and without pain in the ketamine and the control groups. The cut-off value used for the VAS/NRS scales was 3 (range 0–10), which is a generally well-accepted value with clinical impact in view of quality of life.

Results: Our analysis identified ten papers for the comprehensive meta-analysis, including a total of 784 patients. Three papers, which included a total of 303 patients, reported a positive outcome concerning persistent postsurgical pain. In the analysis, only one of nine pooled estimates of postoperative pain at rest or in motion after 1, 3, 6 or 12 months, defined as a value ≥ 3 on a visual analogue scale of 0–10, indicated a marginally significant pain reduction.

Conclusions: Based on the currently available data, there is currently not sufficient evidence to support a reduction in chronic pain due to perioperative administration of ketamine. Only the analysis of postoperative pain at rest after 1 month resulted in a marginally significant reduction of chronic postoperative pain using ketamine in the perioperative setting.

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Abbreviations: IASP, International Association for the Study of Pain; NMDA, *N*-methyl-*D*-aspartate; VAS, Visual Analogue Scale; NRS, Numerical Rating Scale; RR, relative risk; CI, confidence interval; POCP, postoperative chronic pain.

[☆] This work should be attributed to the Department for Anaesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, CH-4031 Basel, Switzerland.

* Corresponding author. Tel.: +41 61 328 6496; fax: +41 61 265 7320.

E-mail address: wruppen@gmail.com (W. Ruppen).

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Implications: It can be hypothesised, that regional anaesthesia in addition to the administration of peri-operative ketamine might have a preventive effect on the development of persistent postsurgical pain. An additional high-quality pain relief intra- and postoperatively as well after discharge could be more effective than any particular analgesic method per se. It is an assumption that a low dose infusion ketamine has to be administered for more than 72 h to reduce the risk of chronic postoperative pain.

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1. Introduction

The development of chronic pain after surgery is a major concern [1]. It has been estimated that acute postoperative pain is followed by persistent chronic pain in 10–50% and that it may be severe in about 2–10% of these patients [2,3]. The socioeconomic burden is considerable, especially if young people with a consequent work disability are concerned.

The International Association for the Study of Pain (IASP) defines chronic postsurgical pain as pain lasting more than the usual wound healing, this may often be more than 3–6 months in absence of other causes [4]. Macrae et al. [5] define it as a short duration of pain, namely 2 months. Ongoing pain for more than 2 months after surgery seems to be a risk factor for persistent pain. Furthermore, a previous study [6] reported pain and hyperaesthesia 6 weeks after breast surgery to be associated with the presence of chronic pain 1 year after surgery.

After the surgical stimulus, acute postoperative pain is driven by nociceptive inputs [1]. Ongoing pain may lead to a delayed and longer lasting, sometimes persistent, phase of central sensitisation [1] leading to hyperalgesia and allodynia as part of a complex neuropathic pain syndrome [3,7,8]. This neuropathic pain syndrome can become chronic. Thus, preventing post-surgical pain

is an important challenge for anaesthetists and surgeons [2,9]. The search for preventive and pre-emptive analgesic treatments with prolonged benefits continues to make slow progress [10]. Therefore, different techniques have been used and studied to decrease the incidence of chronic postoperative pain.

One of the most promising measures preventing chronic pain after surgery is the reduction of central sensitisation by blocking *N*-methyl-D-aspartate (NMDA) receptors with ketamine [3,11]. These receptors have an important role in long-lasting hyperalgesia and in the development of persistent pain [12]. Ketamine has been reported to prevent signs of neuropathic pain in animals [13].

Recent systematic reviews and meta-analyses demonstrate that the NMDA-receptor antagonist ketamine given peri- and intraoperatively can reduce immediate acute postoperative pain, opioid consumption, and opioid-associated side effects such as postoperative nausea and vomiting [14,15]. Furthermore, a previous study demonstrated that a very low dose of intravenous ketamine ≤ 72 h after surgery reduced the incidence of mechanical induced hyperalgesia at the surgical site for at least the first seven postoperative days [16]. As chronic pain has a considerable neuropathic component, ketamine has also been used peri- and intraoperatively to decrease the development of chronic postoperative pain. However, results concerning the role of ketamine to prevent chronic

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