Original Article

British Journal of Pain
2017, Vol 11(4) 166–168

DOI: 10.1177/2049463717736076
journals.sagepub.com/home/bjp

Does perioperative ketamine have a role in the prevention of chronic postsurgical pain: the ROCKet trial

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Abstract
Identifying operations and individuals with an increased risk of chronic postsurgical pain (CPSP) has led to significant interest in interventions with the potential to achieve primary prevention of this condition. Pharmacological prevention remains controversial with a Cochrane review identifying perioperative ketamine administration as the only intervention with possible benefit although, with only small, heterogeneous studies, the authors called for a large randomised controlled trial (RCT) to confirm the validity of this result. In response to these data, a group of researchers from Australia and Hong Kong designed the ROCKet trial – Reduction Of Chronic Post-surgical Pain with Ketamine, endorsed by the Australian and New Zealand College of Anaesthetists (ANZCA) Clinical Trials Network (CTN).

Keywords
Ketamine, chronic postsurgical pain, pain, postoperative, pain management, clinical trial

Over the last 20 years, it has become increasingly obvious that the incidence and severity of chronic postsurgical pain (CPSP) had been poorly recognised and underestimated.[1] As a consequence, significant research efforts have now been directed into identifying the incidence, severity, characteristics and effects of CPSP.

It is now obvious that CPSP is common after all surgery with a high variability in incidence depending on type of surgery (in the range of 10%–70%).[2] The overall average incidence in major surgery is in the range of 12% as shown by a wide range of studies with a variety of designs.[3,4] The pain often has a neuropathic component.[5] The effects of CPSP on the quality of life of those affected are significant, and the costs to healthcare systems and society are high, in particular in view of the large number of surgeries performed worldwide.[1] It is therefore not surprising that a task force of International Association for the Study of Pain (IASP) to advise the World Health Organization (WHO) on the inclusion of chronic pain for the upcoming 11th revision of the International Classification of Diseases (ICD-11) has proposed 'chronic postsurgical and posttraumatic pain' as one of the new classifications.[6]

Attempts to identify risk factors for CPSP have made significant progress and identified a large number of domains of these risk factors.[7] These include demographic factors such as age and gender[2] and genetic factors.[8] With regard to surgery, risk of nerve injury, more traumatic approaches and repeated revisions are relevant risk factors.[9] Psychosocial predisposition is becoming a very obvious and relevant risk

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factor – depression, psychological vulnerability, stress and anxiety, catastrophising and poor coping skills need to be mentioned here.[10] Finally and very relevant are the data confirming that *'pain predicts pain'*;[2] that is, severe chronic preoperative pain, preoperative use of opioids to treat this pain and severe acute postoperative pain are very important risk factors for the development of CPSP.

Identifying operations and individuals with an increased risk of CPSP has lead to significant interest in interventions with the potential to achieve primary prevention of this condition. The findings here are mixed, often contradictory and overall rather disappointing. Best evidence for a preventive role has regional anaesthesia techniques such as epidural analgesia for thoracotomy and continuous paravertebral blockade for mastectomy.[11]

Pharmacological prevention remains controversial. The use of gabapentin and pregabalin perioperatively was initially shown to be an effective preventive strategy;[12] however, subsequent meta-analyses have questioned these findings[13] and a most recent one found no preventive effect on CPSP with pregabalin.[14]

A comprehensive Cochrane review identified a benefit out of all pharmacological interventions to prevent CPSP only for parenteral perioperative ketamine administration (odds ratio (OR): 0.5; 95% confidence interval (CI): 0.33–0.76, p = 0.001 for overall effectiveness on all pain at 6-months follow-up).[13] Ketamine is not surprisingly a promising candidate from a mechanistic point of view; as an N-Methyl-D-aspartate (NMDA) receptor antagonist, it has the potential to reduce spinal cord wind-up and has been shown to have anti-hyperalgesic effects in low doses,[15] making it a useful component of multimodal postoperative analgesia.[16] However, the Cochrane review quoted above is based on an analysis of eight very heterogeneous trials of small size with overall 914 patients enrolled.[13] The authors appropriately caution about the validity of this result and suggest the need for a large RCT.

In response to these data and after subsequent reanalysis of the literature coming to similar findings, a group of researchers from Australia and Hong Kong (Chief Investigator P. Peyton and Principal Investigators K Leslie, D Story, P Myles, M Chan, S Schug, L Evered and S Braat) designed the ROCKet trial – *R*eduction *O*f *C*hronic Post-surgical Pain with *Ket*amine, endorsed by the Australian and New Zealand College of Anaesthetists (ANZCA) Clinical Trials Network (CTN). To assess the feasibility of the trial and its design, a pilot study randomising 80 patients was performed successfully.[17]

The final design of the ROCKet trial is a definitive, large, multicentre, double-blind, placebo-controlled and randomised Phase 3/4 trial of the effect of intravenous ketamine on the incidence and severity of CPSP. This design was submitted as a grant proposal for a 2016 Project Grant to the National Health and Medical Research Council (NHMRC) in Australia. In December 2016, it was awarded the largest NHMRC project grant for 2016 with funding of AU$4,823,395.

In more detail, the ROCKet trial will enrol 4884 patients undergoing abdominal surgery involving an expected skin incision at least 8 cm in length (including open inguinal herniorrhaphy) or non-cardiac thoracic surgery (including mastectomy, breast reconstruction and video-assisted thoracoscopic surgery (VATS) and major orthopaedic surgery (excluding spinal surgery)). Patients will be assessed in detail preoperatively and then randomised to perioperative placebo or ketamine administration, stratified by site and preoperative chronic pain.

Ketamine will be administered as an intravenous (IV) bolus after induction of 0.5 mg/kg, followed by continuous infusion of 0.125 mg/kg/h intraoperatively and postoperatively. Postoperative infusion will be continued for a maximum of 72 h; in view of the pragmatic trial design of ROCKet, ketamine will be discontinued when the patient no longer requires opioid analgesia (IV or oral) for acute pain management or IV access is discontinued by the treating surgical unit or the patient is deemed ready for discharge home by the treating surgical unit.

Primary endpoint is the incidence of CPSP reported by the patient at telephone follow-up structured interview, 12 months after surgery, and adjudicated as CPSP by the endpoint adjudication committee.

There are a large number of secondary endpoints including incidence of CPSP at 3 months, severity of CPSP at 3 and 12 months, incidence and severity of neuropathic symptoms and pain at 3 and 12 months after surgery, disability and quality-of-life estimates, severity of acute postoperative pain, opioid and other analgesic consumption and adverse events. In addition, a health economics analysis will be performed and a genetic bio-repository will be created.

For further details, see: http://medicine.unimelb.edu.au/research-groups/medicine-and-radiology-research/appmu/appmu/the-rocket-study

The trial team can be contacted at: rocket-trial@unimelb.edu.au

Conflict of interest

S. Schug is one of the Principal Investigators and P. Peyton is the Chief Investigator of the ROCKet Trial, which is run through the ANZCA CTN funded by an NHMRC Project Grant.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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