Ketamine for analgesia

Ketamine is a phencyclidine derivative and is a well-established anaesthetic drug with a variety of uses. It is a non-competitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor producing a state of 'dissociative anaesthesia'. Antagonism of the neurotransmitter glutamate from binding to the NMDA receptor results in its analgesic properties.

Wound pain may persist for 3–6 months following surgery (Kehlet et al, 2006). Interest has grown in ketamine as an analgesic in the perioperative period and its potential role in treating persistent pain. Several trials have attempted to gauge the efficacy of ketamine in multimodal analgesia and assess the incidence and severity of side effects.

Nociceptive pain is caused by direct stimulation of specific sensory nociceptors, e.g. heat, sharp. Inflammatory pain is caused by sensitization of pain pathways by mediators (e.g. cytokines, glutamate and serotonin) released in response to tissue damage. This 'inflammatory soup' causes pain until healing occurs. Neuropathic pain is the final type and is caused by nerve or neurotransmission system damage. It results in sensory loss but also hyperalgesia – neuronal plasticity or 'wind-up'. Ketamine appears to work primarily on neuropathic pain whereas opioids and non-steroidal anti-inflammatory drugs work on nociceptive and inflammatory pain.

The case for ketamine

Bell et al (2006) undertook a systematic review of 37 double-blind placebo-controlled trials looking at the effects of ketamine use on morphine consumption, pain intensity, time to first analgesia post-surgery, and adverse effects. All trials used sub-anaesthetic dosing. They found that ketamine significantly reduced morphine patient-controlled analgesia consumption in the first 24 hours and gave a 30–50% decrease in the use of rescue analgesics. Despite nausea and vomiting being a side effect of ketamine being, the review found a significant decrease in postoperative nausea and vomiting with its use compared with that in control groups. This may be because of the decreased opiate use, as these are well known for their emetogenicity.

Sen et al (2009) reported that use of ketamine in abdominal hysterectomy significantly reduced patient-controlled analgesia morphine use and improved patient satisfaction compared with control groups.

Both Menigaux et al (2000) and Remérand et al (2009) found ketamine use during and after orthopaedic surgery reduced morphine consumption and decreased time to initial mobilization. Interestingly, when looking at its use as an infusion following hip arthroplasty, Remérand et al (2009) showed a significant decrease in pain at 6-month follow up. These additional benefits might be of use for enhanced recovery programmes and reducing hospital length of stay.

The case against ketamine

The efficacy of mixed opioid and ketamine patient-controlled analgesia is unclear. Carstensen and Møller (2010) undertook a qualitative review of randomized controlled trials involving the use of mixed opioid and ketamine patient-controlled analgesia *vs* opioid-alone patient-controlled analgesia. Mixed patient-controlled analgesia neither produced better analgesia nor produced more or worse side effects than opioid-only patient-controlled analgesia. Addition of ketamine seems beneficial for thoracic surgery but not necessarily for major abdominal or orthopaedic surgery. The lack of a clear answer might be because of the widely varying concentrations of drugs/mix ratios and patient-controlled analgesia protocols used in these trials.

Although use of ketamine in hospitals is becoming more widespread, there is still resistance to its use. This is usually because health-care staff outside of an anaesthetic or pain environment are not familiar with the drug. There is also a misconception that ketamine will produce terrifying hallucinations and over-sedate patients. In fact, at sub-anaesthetic doses these problems were limited and minor, but the long-term psychological effects of prolonged use are uncertain. Extended abuse of ketamine is associated with bladder atrophy but short-term use does not appear to cause this. Ketamine is a class C drug in the UK, rising in popularity among recreational users. It would be prudent to take measures to prevent abuse, such as the use of locked syringe drivers like those used with patient-controlled analgesia morphine. There is no established optimal dosing regimen for ketamine and so it is down to anaesthetic and acute pain departments to establish this and conduct further research locally.

Conclusions

Ketamine is proven to be safe and has been found to be a good opioid-sparing analgesic. It appears to reduce the risk of chronic postoperative pain developing and its use should be encouraged as part of multimodal analgesia in the perioperative period but more research is needed to establish optimal dosing and the long-term psychological effects. BJHM

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