



Article Appraisal

Article: Low-Dose Ketamine Infusion for Emergency Department Patients with Severe Pain (Pain Medicine. 2015. 16: 1402-1409)

Date of Journal Club: September 7, 2107

Resident Reviewer Name(s) and Residency Affiliation: Dr. Tommy Merth, PGY-3, UBC RCPS-EM Residency

Faculty Methodology/Bio-statistics Resource Person: Dr. Riyad B. Abu-Laban

Background and Study Objective(s):

Ketamine is an increasing focus of EM research as an analgesic adjunct, given its favorable characteristics including rapid onset, a safe hemodynamic profile, and the potential for opioid sparing. Comparatively, opioids have a slower time to peak onset, and potential side effects that include hypotension, sedation, and respiratory depression. How best to administer ketamine, and the effect of this on adverse events, remains a subject of investigation. The objective of this study was to determine the analgesic effect, side effects, and patient acceptance of a ketamine protocol in ED patients with acute, severe pain. The investigators hypothesized that a low dose ketamine bolus followed by a continuous infusion would provide clinically significant and sustained pain relief, be well tolerated, and be feasible among ED patients.

Study Design:

This was a prospective case series of non-randomized ED patients with acute pain who were administered ketamine in a non-blinded fashion with no control group. A ketamine bolus of 15mg IV, followed by an infusion of 20mg over 1 hour, was evaluated. The study was carried out in a single urban teaching hospital, and convenience sampling was used. ED patients 18 years or older, with moderate to severe pain (5/10 or greater on a pain scale), and the ability to consent in English or Spanish were eligible. A change in pain score of 3/10 or more was deemed to be clinically significant. Exclusion criteria were: inability to consent, evidence of traumatic brain injury, poorly controlled hypertension not attributable to pain, history of coronary artery disease, unexplained tachycardia, severe psychiatric disorder, pregnancy, in custody of law enforcement, intoxication with alcohol or other drugs, and weight less than 40kg. Previous analgesia during the ED visit was not an exclusion. Participants were offered morphine 4mg IV at 20, 40, and 60 minutes. Pain intensity, heart rate, SPO₂, sedation, side effects, and adverse events were assessed at multiple time points up to 120mins.

Results:

Forty participants with mean age of 43 years were enrolled over 8 months; 2 were excluded for missing data. Pain causes were diverse, with the most common being abdominal pain, and 58% of participants received analgesics prior to study enrollment (most IV hydromorphone or morphine). The median initial pain score was 9/10. At 10-minutes

post study drug, 57% of participants had a significant reduction in pain; at 60 minutes, 65% of participants had a significant reduction; and at 120 minutes, 67% had a significant reduction. A large proportion of participants were administered morphine during the study period (at 20, 40 and 60 minutes, 42%, 50% and 28% respectively). Vital signs were generally stable, with 3 patients experiencing asymptomatic rises in systolic blood pressure. Of 456 observations for sedation, 20 identified moderate sedation, and the remainder were all minimal. Mild or moderate side effects including dizziness, fatigue and headache, were common (53% of participants) and 34% of participants experienced very bothersome side effects. 84% of participants indicated they would have ketamine again for pain control.

Validity of Results:

Given the lack of a control group, the potential for confounding, and the lack of blinding, Journal Club attendees raised numerous concerns regarding validity of the study results. As a result, although the study suggests a beneficial effect may exist from ketamine, Journal Club attendees felt it was difficult to confidently comment magnitude of the effect, if any, that ketamine had had on pain control in the study participants. Secondary outcomes focused on side effects and how well tolerated ketamine was. Although the authors concluded that the ketamine was well tolerated, Journal Club attendees found it noteworthy that 34% of participants experienced very bothersome side effects, and approximately 1 in 6 said they would not want ketamine again. Discussion ensued, with positive and negative anecdotal accounts brought forward, regarding how side effects from ketamine merited consideration, and would need to be compared to opioids and other forms of analgesia before routine use was advocated. This led to discussion on how methodologically weak designs such as this study are commonly seen early in the evaluation of new modalities and therapies. Recently published research on ketamine, as well as planned research at UBC, was also commented on, in an effort to interpret the study results in a “Bayesian manner” that also considered the totality of the evidence to date on this emerging topic.

Generalizability of Results:

Most Journal Club attendees felt that the results of this study were generalizable to our local population. Limited demographic information was provided, but the positive and negative effects of ketamine were deemed to likely be similar and, other than sickle cell crisis, the pain patterns of patients receiving ketamine in the study appeared similar. It was noted however, that our local population includes a large proportion of intoxicated patients, and patients with a psychiatric history. Many such individuals have opioid use disorders, and may be hypothesized to disproportionately benefit from ketamine. It was noted that dosing of opioids in such patients is often difficult, and some EPs are reluctant to even use opioids in this population. Furthermore, patients taking suboxone may not respond to opioids. Unfortunately the study did not include many such individuals, and challenges securing REB approval for research on this patient population were noted.

The Bottom Line:

This was not felt to be a practice altering article, but rather a step in the evolution of evidence of the ED use of Ketamine for analgesia, a concept that seems likely to become increasingly prevalent. It was expected that this study will not alter current use or non-use of ketamine for ED analgesia by most physicians. The side effects of ketamine found in this study were felt to be significant, the magnitude of ketamine-attributable analgesia was unclear, and patients who may benefit the most from ED ketamine were not enrolled. It was noted that there is currently enthusiasm at Lion’s Gate Hospital for administering ketamine as an analgesic adjunct at a dose of 0.2-0.3 mg/kg over 15 minutes without a longer infusion, and evidence exists that this results in a better side-effect profile. Further research will be required before dosing regimens can be clarified, or widespread incorporation of ED ketamine can be advocated. At this point, most would consider ketamine a potential analgesic adjunct only in highly selected patients.