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Ketamine Infusion for Pain Control in Adult Patients with Multiple Rib Fractures: Results of a Randomized Control Trial

Carver TW, Kugler NW, Juul J, Peppard WJ, et al. *J Trauma Acute Care Surg*. 2019;86(2):181-188. doi:10.1097/TA.0000000000002103

Link to Article: https://pubmed.ncbi.nlm.nih.gov/30376537/

Context

This randomized controlled trial investigates the efficacy of ketamine infusion for pain management in patients with traumatic rib fractures. Due to concerns surrounding the use of opioids for pain management in this population, alternate methods of pain control have been subject to exploration. Recent studies have demonstrated ketamine's utility as an adjunctive therapy for postoperative analgesia and for rib fracture pain control.[1,2] As the existing literature is scarce and primarily retrospective in nature, this study sought to elucidate the effectiveness of ketamine for pain management in the setting of traumatic rib fractures by measuring reduction in numeric pain score (NPS).

Methods

- Single-center, prospective, randomized, double-blind, placebo-controlled trial conducted from August 2015 to December 2017 at an American College of Surgeons verified Level 1 trauma center (Froedtert Memorial Lutheran Medical Center, Milwaukee, WI)
- Primary Outcome: reduction in NPS at 24 hours after initiation of infusion; this institution utilizes a standard 11-point NPS
- Secondary Outcomes: reduction in NPS at 48 hours, opioid consumption in oral morphine equivalents (OME) at 24 hours and 48 hours, total OME, intensive care unit length of stay (ICU-LOS), and hospital LOS (H-LOS), epidural placement rate, pulmonary complications, and other adverse events (nausea, pruritis, respiratory depression, sedation level, presence of disturbing dreams/hallucinations)
- Inclusion Criteria: adult patients sustaining blunt trauma with three or more rib fractures
- Exclusion Criteria: 65 years of age or older, personal history of adverse reaction to ketamine infusion, Glasgow Coma Scale of 13 or less, active acute coronary syndrome, severe hypertension (defined as prolonged systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 100 mmHg), current use of monoamine oxidase inhibitors, chronic opioid use (defined as 30 mg or greater oral morphine equivalents per day for 3 or more weeks), current opiate (prescription and/or heroin) or ketamine abuse, inability to communicate with staff, personal history of psychosis, use of three or more psychotropic medications, active delirium, dementia, glaucoma, pregnancy, and prisoners
- Patients were randomized within 12 hours of arrival to receive either an infusion of low-dose ketamine (LDK) (defined as 2.5 μg/kg/min) or a similar volume of 0.9% sodium chloride based on ideal body weight
- Patients were also managed with usual care (i.e., opiate and non-opiate-based [including oral acetaminophen, nonsteroidal anti-inflammatory medications, and muscle relaxants])

medication regimens and were followed throughout their admission and for 30 days after discharge
- Participants, providers and all study staff were blinded to subject assignments
- Clinically significant reduction (i.e., minimal clinically important difference) in NPS was defined as a 2-point reduction on an 11-point scale based upon the literature and variation based on institutional pilot data
- Power: sample size of 91 (45 in LDK group and 46 in placebo group)

Findings
- 933 patients were assessed for eligibility and 92 were randomized – 46 in the LDK group and 46 in the placebo group; 1 participant withdrew from the study, resulting in 45 patients remaining in the LDK group. Fourteen patients completed less than 24 hours of infusion
- Demographics: 74.7% male, median age of 49, median ISS of 14, most common mechanism of injury was motor vehicle collision (45.7%); no significant difference in demographic or injury characteristics
- Intercostal nerve blocks were performed in similar proportions of LDK and placebo patients (11 (24.4%) LDK patients and 13 (28.3%) placebo patients)
- There was no difference in epidural placement between the LDK and placebo groups (15.6% vs. 6.5%; p=0.18)
- There was no difference in NPS reduction at 12-24 hours (p=0.36) or at 24-48 hours (p=0.77)
- There was no significant difference in the use of non-opioid pain medications or adverse events between the two groups
- Subset analyses:
    - LDK did not reduce NPS or OME in patients with isolated rib fractures
    - LDK did not reduce NPS or OME in patients admitted to the ICU
    - LDK did not reduce NPS in patients with ISS greater than 15
    - LDK reduced OME in patients with ISS greater than 15 at 12-24 hours [50.5 (47.2) vs. 94.3 (74.3); p=0.03] and at 24-48 hours [87.0 (126.1) vs. 164.1 (259.0); p=0.03]

Commentary
The results of the present study did not demonstrate a reduction in NPS at 24 hours (primary outcome) or reductions in secondary outcomes, including NPS at 48 hours, opioid consumption (OME) at 24 hours or 48 hours with the use of LDK. While this may be generally interpreted as a negative study for the analgesic value of LDK beyond usual care, there are several considerations worth discussing.

In exploratory evaluation, there was a reduction in the utilization of OME in patients with an ISS of 15 or greater. As this trial was conducted at a Level 1 trauma center where patient injuries often extend further than rib fractures alone, the reduction of OME use in patients administered LDK at this facility is suggestive of a beneficial effect of LDK in the setting of cumulative injuries. However, the presence of injuries in addition to rib fractures was not able to be determined in this study. In the subset analysis stratifying by injury severity, patients with an ISS ≥15 who received LDK showed decreased OME utilization when compared to placebo. As the

study population consists of patients with a mean ISS of 14 who are all being managed with a baseline multimodal pain control regimen, the possibility that the effect of LDK is underestimated in more severely injured patients should be considered.

The adverse effect profile of LDK was demonstrated to be insignificant, which is likely explained by adverse effects seen with higher doses (up to 4.5 mg/kg) necessary to obtain procedural sedation rather than the lower doses needed to achieve pain control.[3] Ketamine also plays a role in blunting the physiologic response to pain by antagonizing NMDA receptors, further suggesting a role for this therapy in the management of neuropathic and chronic pain.[4,5] As this study opted to utilize 2.5 μg/kg/min with an effect demonstrated only in severely injured patients, the question remains as to whether the dose could be reasonably increased to optimize pain control while still mitigating the risk for adverse effects. In a Cochrane review which showed favorable effects of LDK in postoperative patients, dosages ranged from 2 μg/kg/min to 1 mg/kg/min.[4] With this range of dosing, consideration should be made for the use of modestly higher doses of LDK in providing more efficacious pain management in trauma patients.

Lastly, the utility of NPS, a subjective measure, as the primary outcome of this study may have influenced the findings, particularly in the setting of multiple injuries. The investigators were unable to account for this by separating thoracic and global pain scores due to inconsistencies between the different pain scoring systems. Also, the lack of a standardized pain management regimen and the allowance of providers to control pain with additional medications permitted by their institution's rib fracture pain management order set (ex. Oral acetaminophen, etc.) may have affected the findings of this study, although it is less likely as the results demonstrated no difference in non-opiate pain medication administration between the two groups. Lastly, the protocol of the institution did not allow for the investigators to titrate the ketamine infusion, only allowing for ketamine infusion to be set at a fixed low dose of 2.5 μg/kg/min. Due to variations in dosing between this study and others, future investigations may seek to determine the optimal dosing of ketamine in the management of pain secondary to traumatic rib fractures.[4]

Implications

Despite their potential for abuse and dependence, opioids remain the cornerstone of pain control in patients suffering from traumatic rib fracture.[6] This randomized controlled trial investigated the use of LDK as an adjunctive medication for pain control to determine if this regimen would be effective in reducing pain and OME in these patients. Though no difference in NPS was noted in the results, a reduction in OME was demonstrated in patients with an ISS of 15 or greater. Though further investigation is warranted, this finding suggests a potential role of LDK as an adjunctive medication for pain control in the setting of rib fractures and multiple-injury trauma.

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