**CRITICAL REVIEW FORM: THERAPY ARTICLES**

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**Citation:**

Alshahrani, M. S., et al. Ketamine administration for acute painful sickle cell crisis: a randomized control trial. *Academic Emergency Medicine.* 2021;00:1-9.

**Study Objective:**

“To evaluate the efficacy and safety of single-dose ketamine infusion in adults with sickle cell disease who presented with acute sickle cell vaso-occlusive crisis.”

Primary outcome: mean difference in the numerical pain rating scale (NPRS) over 2 hours (compared to morphine group)

Secondary outcomes:

* Cumulative dose of opioids
* ED LOS
* Hospital admission
* VS changes
* Drug-related side effects

**Study Methodology:**

* Prospective RCT
* Parallel groups - randomized to single dose of ketamine or morphine
* Single-center: ED at King Fahd Hospital
* Large tertiary care center in Eastern Province of Saudi Arabia
* Patients: 18+ yo adults with SCD and NPRS > 5
* Confirmed HgB electrophoresis
* Onset of symptoms <7 days prior to presentation
* Exclusion criteria:
* Pregnant/breast-feeding
* BMI >40
* Hx neurologic disease, seizure, acute head injury, psychiatric disorder
* Hx cardiac disease, pulmonary disease, renal disease, liver disease
* Allergy to study drugs
* Sepsis/shock, ventilator support
* Alcohol/drug abuse
* Chronic pain unrelated to SCD
* Randomized using computer program
* Concealed randomization and treatment allocation
* Participants, HCPs, data collectors, and outcome assessors blinded
* Bedside nursing giving meds also blinded
* **Initially all patients presenting with VOC were given either acetaminophen 1 g IV or NSAID (lornoxicam/diclofenac) at physician discretion**
* 30 minutes later, patients with NPRS > 5 were enrolled
* Ketamine 0.3 mg/kg vs morphine 0.1 mg/kg
* Mixed in 100 cc NS bag
* Patients discharged after min. 120 minutes or admitted within 180 minutes

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| **GUIDE** | **COMMENTS** |
| * **Are the results valid?**
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| * **Did experimental and control groups begin the study with a similar prognosis?**
 | Yes. Both VOC pain from SCD and patients with a number of medical comorbidities were excluded. Both groups with NPRS > 5 at time of enrollment. |
| * Were patients randomized?
 | Yes, using computer program |
| * Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be “randomized” to a particular group?
 | Based on what is reported, blinding seems to be quite good. An independent study nurse randomized patients, labeled the medication bags, and handed them to blinded bedside nurses. Physicians were blinded as well. |
| * Were patients analyzed in the groups to which they were randomized? (*intention-to-treat analysis*)
 | Yes, intention-to-treat analysis was performed, and it seems all 278 study participants were analyzed in their respective groups. |
| * Were patients in the treatment and control groups similar with respect to known prognostic factors?
 | Yes, generally. |
| * Were patients aware of group allocation?
 | No, however in a patient who has received morphine in the past it is not unreasonable to think they may have been able to notice a difference in subjective experience of ketamine |
| * Were clinicians aware of group allocation?
 | No, but going along with previous, patients could have made comments to clinicians regarding their perception of the treatment drug which could potentially key clinicians into which treatment was received. There is no mention regarding physicians' direct interaction with patients. |
| * Were outcome assessors aware of group allocation?
 | No |
| * Was follow-up complete?
 | Follow-up was complete, as patients were either admitted or discharged (secondary outcome) |
|  **II. What are the results?** | Ketamin non-superior to morphine in improving pain scores in SCD VOC with comparison of single dose. Ketamine did reduce the cumulative dose of opioid medication. No difference in adverse affects, hospitalization, or VS changes. |
| * How large was the treatment effect?
 | No reduction in pain scores in ketamine compared to morphine. Cumulative dose of morphine reduced 0.06 mg/kg in ketamine group. |
| * How precise was the estimate of the treatment effect? (CIs)
 | NPRS CI (-0.34 to 0.60)Cumulative opioid dose CI (.038 to 0.083)Very wide CI for primary outcome which was not significant. Narrow CI for secondary outcome of cumulative opioid use with small reduction in cumulative dosing. |
|  **III. How can I apply the results to patient care?** |  |
| * Were the study patients similar to my patient?
 | SCD patients are common anywhere, however chronic pain management may differ in Saudi Arabian population. The location in a tertiary care center is similar to SNGH. Different ethnic populations. |
| * Were all clinically important outcomes considered?
 | I think most were, however cost was not addressed. An analysis of cost between two groups would add to comparison and clinical significance of ketamine vs opioid. |
| * Are the likely treatment benefits worth the potential harm and cost?
 | In the context of the study there does not seem to be any difference in potential harm. In fact, there is theoretical benefit to less opioid dosing.  |

**Limitations:**

* Dosing of medications
* Doses given in IV push bags - not typical for many EDs
* Single center study
* Limited external validity
* Potential for unblinding from patient reactions, comments, and symptoms
* Fixed ketamine dosing - single dose compared to single dose morphine though with potential for repeat opioid dosing

**Clinical Bottom Line:**

In a single-center RCT, ketamine was not superior compared to morphine in reducing pain scores in patients presenting with vaso-occlusive crisis from SCD. However, ketamine use did decrease the cumulative dosing of opioids (i.e. morphine) without affecting hospital admission or producing increased adverse events. The study was well constructed and well-blinded, however opportunities for unblinding may have existed. Based on the results, ketamine is a viable option in treating SCD VOC and may have benefit in reducing the total amount of opioid dosing, without significantly out-performing morphine in pain control.