AAEM Clinical Practice Statement

Is There a Role for Intravenous Sub-Dissociative-Dose Ketamine Administered as an Adjunct to Opioids or as a Single Agent for Acute Pain Management in the ED? (9/6/2015)

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INTRODUCTION:

Sub-dissociative dose ketamine (low-dose ketamine) is useful and safe to use alone or in combination with opioid analgesics for the treatment of acute pain in the Emergency Department (ED) and in pre-hospital settings. Its use is associated with higher rates of minor but well tolerated adverse side effects.

In order to identify manuscripts for review a PubMed query was carried out by using the following terms: "low-dose ketamine, “sub-dissociative dose ketamine" "acute pain in the ED", and "analgesia in the ED". Only randomized controlled trials, systematic reviews, meta-analyses and observational studies were included. Case series and reports were excluded as well as studies evaluating the intranasal route of ketamine administration (due to dosing variability.) Systematic reviews with inconclusive results (neither supporting nor refuting the use low-dose ketamine) were also excluded. The search was limited to the English language, and included only adult human studies in patients not older than 65 years of age. We limited the search to include studies done only in the five years between 2010-2015. Based on these search parameters 8 studies were included in the final analysis.

EXECUTIVE SUMMARY

The provision of adequate safe and timely analgesia is a core component of patient care in the emergency department (ED.) Ketamine is a non-competitive Nmethyl-D-aspartate (NMDA) and glutamate receptor antagonist that provides analgesia, antihyperalgesia, and antitolerance by virtue of decreasing central sensitization, “wind-up” phenomenon, and pain memory. Ketamine, at sub-dissociative doses of 0.1-0.4 mg/kg (also known as low-dose ketamine, or analgesic-dose ketamine), provides effective analgesia without serious adverse effects and preserves protective airway reflexes, spontaneous respiration, and cardiopulmonary stability. In sub-dissociative doses ketamine has been shown to be effective in providing analgesia while reducing the need for opioids in the treatment of acute traumatic and non-traumatic pain, chronic pain, and in opioid-tolerant pain patients in a pre-hospital setting and in the ED. The tradeoff for obtaining effective analgesia and decreasing opioid administration when using sub-dissociative dose Ketamine is the relatively high rate (14%-80%) of minor adverse side effects.

Given the concerns of serious opioid-related adverse effects and the limited analgesic effects of opioids in patients with chronic and opioid-tolerant pain, the administration of ketamine at sub-dissociative doses as an adjunct to opioids, or as a single agent, results in better pain control with less potential for serious adverse effects. In this paper we address the role of sub-dissociative-dose ketamine administered as an adjunct to opioids and as a single agent for the acute management of pain in the ED.

Discussion

Sub-dissociative-dose Ketamine analgesia has gained a great deal of attention in the emergency medicine literature over the last five years as a viable analgesic modality. A prospective pre-hospital cohort study compared intravenous morphine (0.2mg/kg) alone to the combination of intravenous morphine-ketamine (0.1 mg/kg and 0.2 mg/kg) and demonstrated a significantly greater improvement in pain scores upon arrival of patients to the hospital in the morphine-ketamine group (3.1 vs.5.4) with a significantly decreased total dose of morphine required in the morphine-ketamine group (7 mg vs. 13.5 mg). Fourteen percent of the patients had minor adverse side effects related to ketamine administration (dizziness and a feeling of "unreality")[1]. Similarly, another pre-hospital prospective randomized controlled trial of patients with traumatic pain reported better pain relief and had a greater change in the pain score upon hospital arrival when comparing the use of IV morphine+ketamine to IV morphine alone (3.2 vs. 5.6). There were higher rates of minor adverse side effects in the combined treatment group, mainly nausea and dizziness. (39% vs. 14%). [2]. A systematic review evaluating pre-hospital ketamine analgesia looked at 6 relevant articles and concluded that ketamine analgesia when used with morphine provides effective and safe pain relief while reducing the amount of morphine required. One study demonstrated significant rates of neuropsychological adverse effects (54% of patients) which included hallucinations, dizziness, diplopia and dysphoria. These adverse side effects were brief in duration and weak in intensity and did not require any treatment interventions.[3,4]

Several other well-designed trials in the ED evaluated the analgesic efficacy, safety, and opioid sparing effects of intravenous sub-dissociative**-**dose ketamine for acute pain control. In a prospective observational study of adult patients with severe pain who received IV ketamine (15mg) and half-dose IV hydromorphone (0.5 mg), 46% of the patients had complete pain relief at 5 minutes with 80% of the patients reporting the minimal or modest adverse side effects of nausea, dizziness, and a feeling of unreality. [5] Another randomized double-blind, placebo-controlled trial evaluating the analgesic efficacy and safety of low-dose ketamine (0.15 mg/kg and 0.3 mg/kg) administered intravenously as an adjunct to opioids for patients with acute moderate to severe pain reported significantly greater pain relief in the ketamine/morphine combinations than morphine alone. Patients receiving the ketamine/morphine combination reported a sustained reduction in pain intensity for up to 2 hours but more of these patients reported a feeling of "unreality" and dizziness as the adverse side effects of the treatment.[6].

Another prospective randomized trial comparing low-dose intravenous ketamine (0.3 mg/kg) to intravenous morphine (0.1 mg/kg) in 45 emergency department patients with acute abdominal, flank, low back, or extremity pain demonstrated a faster onset of analgesia (5 min) in the ketamine group and was comparable to pain control of morphine alone at 20 minutes. The rates of adverse effects were similar in the two groups (58% vs.57) however, at 20 minutes from the initial administration of ketamine 54% of patients needed a

second dose of ketamine (0.3 mg/kg.) In comparison 38% of the patients in the morphine group also required a second dose of medication (0.1 mg/kg.) This study demonstrated the value of LDK in controlling acute pain in the ED when compared to IV morphine by providing significant pain relief at 5 minutes and a moderate reduction of pain for 2 hrs. [7].

A similarly designed trial compared intravenous sub-dissociative-dose ketamine (0.3 mg/kg) to intravenous morphine (0.1 mg/kg) for acute pain in the ED and demonstrated no significant difference in the change in mean pain scores at the baseline (8.6 vs, 8.5) and at 30 minutes from treatment (4.1 vs. 3.9.) Importantly, more patients in the ketamine group reported complete resolution of pain at 15 minutes (44% vs. 13%). Nearly three fourths of the patients in the ketamine group had transient minor adverse side effects at 5 minutes (73% vs. 51)% and 15 minutes (69% vs. 31%), including nausea, dizziness and a feeling of unreality. These adverse effects did not require any treatment or interventions. .[8].

CONCLUDING STATEMENT

The use of intravenous sub-dissociative dose ketamine administered either alone or in combination with opioids is safe and effective for the treatment of acute pain in the ED allowing for reduced opioid administration. Its use has been associated with relatively high rates of minor and short lived adverse side effects.

NOTE: The authors certify that they have no real or apparent conflict of interest to with regard to the content of his paper.