

# Utilization of Ketamine for Acute Pain in the Prehospital and Emergency Department Setting: A Preliminary Meta-Analysis of the Evidence

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## Background

Tactical Combat Casualty Care (TCCC) guidelines recommend use of ketamine as an option to manage moderate to severe pain on the battlefield for casualties in or at risk for hemorrhagic shock or respiratory distress.

Medics are required to withdraw doses from multi-dose vials, which can be challenging in the combat setting.

This project may contribute to evidence for submission to the FDA in support of obtaining an analgesic indication for ketamine, so that the development of auto injectors may be pursued.

## Objective

The purpose of this project was to identify and summarize best evidence related to the administration of ketamine for acute pain in the pre-hospital and emergency department (ED) settings.

1. How does ketamine compared to placebo or other pain medications influence pain relief?
2. What is the recommended dosing of ketamine?

## Methods

- **Databases searched:** Medline Plus, Cochrane, EMBASE, DTIC, Google Scholar, Merck Index, PsychINFO, and Academic Search Ultimate.
- **Keywords:** ketamine, prehospital, emergency department, emergency medicine, acute pain, analgesic, analgesia
- **Inclusion Criteria:** 1) Randomized Controlled Trials (RCTs); 2) Compared the analgesic effect of IN, IM, IV ketamine to opioids or placebo; 3) Reported reductions in numeric rating scores (NRS) or visual analogue scale scores (VAS); 4) Sample limited to ED or out-of-hospital patients; 5) Participants at least 18 years of age
- **Data Analysis:** Ketamine dosage amounts and NRS/VAS scores were extracted and used to calculate a summary statistic for dosage, and overall effect size for subgroups (standardized mean difference with 95% CI).

## Results

Table 1 – Summary of the Study Characteristics

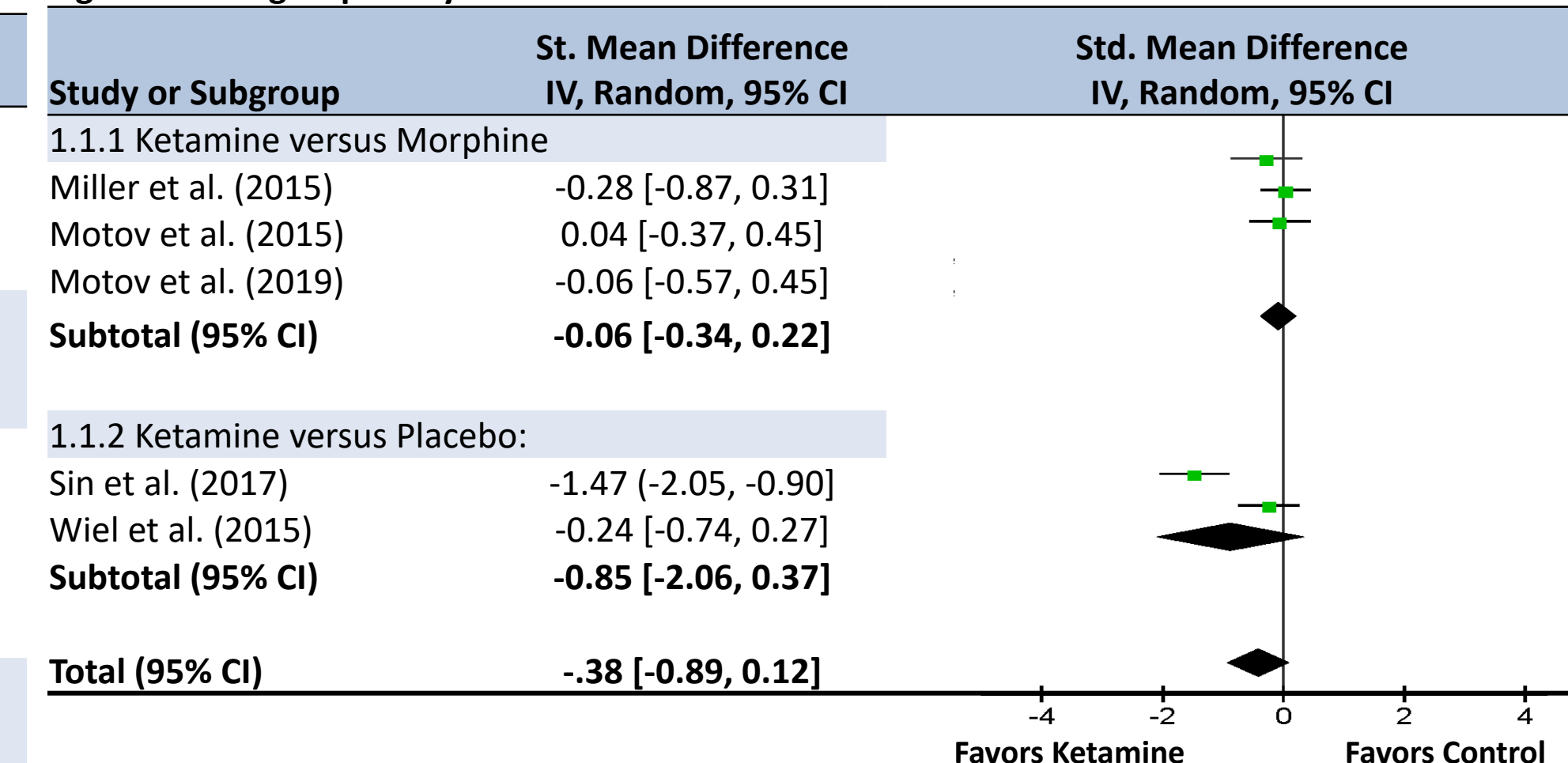
Study	Sample Characteristics	Administration	Ketamine Dosage	Blind
Miller et al. (2015)	ED patients with moderate-severe acute abdominal, flank, low back, or extremity pain.	Intravenous	0.3 mg/kg	Double-blind
Motov et al. (2015)	ED patients with acute abdominal, flank, back, or musculoskeletal pain.	Intravenous	0.3 mg/kg	Double-blind
Motov et al. (2019)	ED patients with moderate to severe acute ab, flank, musculoskeletal, or malignant pain.	Intravenous	0.3 mg/kg	Double-blind
Sin et al. (2017)	ED patients reporting moderate to severe acute pain.	Intravenous	0.3 mg/kg	Double-blind
Wiel et al. (2015)	ED patients with isolated orthopedic injuries secondary to trauma, reporting severe acute pain.	Intravenous	0.2 mg/kg	Single-blind (participants)

- Total of 347 patients from five studies
  - $N = 186$  for morphine comparison studies ( $n = 3$ )
  - $N = 121$  for placebo-controlled studies ( $n = 2$ )
- Patients age ranged from 18 to 75
- **Median ketamine dosage: 0.3 mg/kg (IQR: 0.28 - 0.30)**

## Limitations

- Sample of studies for preliminary analysis were small.
- For placebo-controlled group, studies' effect sizes were so dissimilar that there may be an underlying factor influencing the difference.
- Did not test for potential moderators (e.g., injury severity) of effect size for placebo-controlled group.

Figure 1 – Subgroup Analysis of Pain Difference



- **Ketamine versus Morphine**
  - Overall effect was in favor of ketamine (SMD = -0.06,  $p = 0.66$ ).
  - Studies were homogenous ( $\chi^2 (2) = .76$ ,  $p = 0.68$ ,  $I^2 = 0\%$ ).
- **Ketamine versus Placebo**
  - Overall effect was in favor of ketamine (SMD = -0.85,  $p = 0.17$ ).
  - Studies were heterogeneous ( $\chi^2 (1) = 10.07$ ,  $p = 0.002$ ,  $I^2 = 90\%$ ).
- **Subgroups** were not significantly different ( $\chi^2 (1) = 1.52$ ,  $p = 0.22$ ,  $I^2 = 34.2\%$ ).
- **Ketamine versus either Morphine or Placebo**
  - Overall effect was in favor of ketamine (SMD = -0.38,  $p = 0.14$ ).
  - Studies were heterogeneous ( $\chi^2 (4) = 19.52$ ,  $p < .001$ ,  $I^2 = 80\%$ ).

## Conclusions

Results from this preliminary analysis imply ketamine is efficacious in comparison to no pain medication or to other pain medications. Results also suggest a dosage of 0.3 mg/kg is common in the treatment of acute pain in the ED, however further analyses are needed to determine optimal dosages.

## Acknowledgements

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