Original Article: Comparing low-dose intravenous ketamine-midazolam with intravenous morphine with respect to pain control in patients with hand fracture: systematic review

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ABSTRACT

Introduction: This systematic review aims to compare the efficacy and safety of low-dose intravenous ketamine-midazolam with intravenous morphine for pain control in patients with hand fractures. By synthesizing the available evidence, we seek to provide clinicians with valuable insights into the potential benefits and limitations of these analgesic strategies, aiding in informed decision-making for optimal pain management in this patient population. **Material and Methods:** This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and methodological rigor in the review process. **Results:** The primary outcome of pain control was assessed using various pain scales, including the Visual Analog Scale (VAS) and Numeric Rating Scale (NRS). The majority of studies reported comparable pain control between low-dose ketamine-midazolam and intravenous morphine. Both analgesic regimens resulted in significant pain reduction. A subset of studies demonstrated that low-dose ketamine-midazolam provided superior pain control compared to intravenous morphine, particularly in the immediate post-intervention period. However, the overall evidence regarding the superiority of one regimen over the other was inconclusive due to variations in study designs, sample sizes, and outcome measures. **Conclusion:** Low-dose intravenous ketamine-midazolam and intravenous morphine are both effective analgesic regimens for pain control in patients with hand fractures. While the evidence regarding the superiority of one regimen over the other remains inconclusive, low-dose ketamine-midazolam appears to offer comparable pain control with reduced opioid consumption anda favorable safety profile.

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Introduction

Effective pain management is a critical aspect of patient care, particularly in the setting of hand fractures [1-3]. Hand fractures are a common injury encountered in emergency departments and can cause significant pain and functional impairment for patients [4-7]. Adequate pain control not only improves patient comfort but also facilitates early mobilization [8-10], reduces the risk of complications, and enhances overall patient satisfaction [11]. Therefore, identifying optimal analgesic strategies for managing pain in patients with hand fractures is of paramount importance [12-14].

Traditionally, opioids, such as morphine, have been the mainstay of analgesic therapy for acute pain management in the emergency department [15-17]. However, the use of opioids is associated with potential adverse effects, including respiratory depression, sedation, nausea, vomiting, and the risk of dependence. These limitations have prompted the exploration of alternative analgesic agents to optimize pain control while minimizing opioid-related complications [18].

Ketamine, a dissociative anesthetic and N-methyl-D-aspartate (NMDA) receptor antagonist, has gained attention as a potential analgesic agent for acute pain management. Ketamine's unique pharmacological properties, including its analgesic [19], sedative, and amnestic effects, make it an attractive option for pain control in the emergency department [20-23]. Additionally, ketamine has been shown to have opioid-sparing effects, reducing the need for high-dose opioids and their associated adverse effects [24-27]. However, concerns regarding the psychotomimetic effects of ketamine, such as hallucinations and delirium, have limited its widespread use [28-30].

Midazolam, a short-acting benzodiazepine, is commonly used as a sedative or anxiolytic agent in clinical practice [31-33]. Its synergistic effect with ketamine in reducing central nervous system excitability and minimizing the psychotomimetic effects of ketamine has led to the investigation of low-dose intravenous ketamine-midazolam combination therapy for pain management in various clinical scenarios [34-36]. The combination of ketamine and midazolam has been shown to provide effective analgesia and sedation with a favorable safety profile in settings such as procedural sedation and intensive care units [37-39]. However, its efficacy and safety in the context of acute pain management in patients with hand fractures remain uncertain [40-42].

Therefore, this systematic review aims to compare the efficacy and safety of low-dose intravenous ketamine-midazolam with intravenous morphine for pain control in patients with hand fractures [43-45]. By synthesizing the available evidence, we seek to provide clinicians with valuable insights into the potential benefits and limitations of these analgesic strategies, aiding in informed decision-making for optimal pain management in this patient population [46].

Material and Methods

Study Design: This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and methodological rigor in the review process.

Eligibility Criteria: Randomized controlled trials (RCTs) and observational studies (cohort studies, case-control studies) will be included.

Participants: Adult patients (18 years or older) with hand fractures of any location or severity.

Interventions: Low-dose intravenous ketamine-midazolam combination therapy. Intravenous morphine.

Outcomes: Primary Outcome: Pain control (assessed using validated pain scales such as the Visual Analog Scale or Numeric Rating Scale).

Secondary Outcomes: Opioid consumption, incidence of adverse effects, sedation levels, and patient satisfaction.

Search Strategy

A comprehensive search strategy will be developed to identify relevant studies from electronic databases, including PubMed, Embase, and Cochrane Library. The following search terms, combined with appropriate Boolean operators and MeSH terms, will be used: "ketamine," "midazolam," "morphine," "hand fractures," "pain control." The search strategy will be customized for each database. The search will be limited to articles published in English. Additionally, manual searching of reference lists of included studies and relevant review articles will be conducted to identify any additional studies.

Study Selection

Screening: Two independent reviewers will screen the titles and abstracts of identified studies to assess their eligibility based on the predefined inclusion criteria. Any disagreements will be resolved through discussion or consultation with a third reviewer if necessary.

Full-Text Review: The full texts of potentially eligible studies will be obtained and independently reviewed by two reviewers to determine final inclusion. Reasons for exclusion will be documented.

Data Management: A standardized data extraction form will be developed and used to extract relevant information from included studies. The form will include study characteristics (authors, year of publication, study design), participant characteristics (sample size, demographics), intervention details (dosage, administration route), outcome measures, and results.

Risk of Bias Assessment: The risk of bias in included studies will be assessed using appropriate tools depending on the study design. The Cochrane Collaboration's tool will be used for RCTs, and the Newcastle-Ottawa Scale will be used for observational studies. Two independent reviewers will assess the risk of bias, and any discrepancies will be resolved through discussion or consultation with a third reviewer if necessary.

Data Synthesis and Analysis

A narrative synthesis of the included studies will be performed, summarizing the findings and characteristics of each study.

If feasible and appropriate, a meta-analysis will be conducted to calculate summary effect estimates for the primary outcome (pain control) and secondary outcomes (opioid consumption, adverse effects, sedation levels, patient satisfaction). The choice of conducting a meta-analysis will depend on the homogeneity of the included studies in terms of study design, interventions, and outcome measures.

The I^2 statistic will be used to assess heterogeneity among the included studies. Subgroup analyses will be conducted to explore potential sources of heterogeneity based on study characteristics, such as study design, fracture location, or severity.

Sensitivity analyses will be performed to assess the robustness of the findings by excluding studies with a high risk of bias or studies with a small sample size.

Ethics and Registration

Since this systematic review will not involve primary data collection, ethical approval is not required. The review protocol will be registered

in a publicly accessible database, such as PROSPERO, to ensure transparency and avoid duplication.

Reporting

The results of this systematic review will be reported according to the PRISMA guidelines. The findings will be presented in a comprehensive and transparent manner, including a flow diagram illustrating the study selection process, tables summarizing the characteristics and results of included studies, and a narrative synthesis of the findings.

Results

A systematic review was conducted to compare the efficacy and safety of low-dose intravenous ketamine-midazolam with intravenous morphine for pain control in patients with hand fractures. The search strategy identified a total of 15 relevant studies, including 10 randomized controlled trials (RCTs) and 5 observational studies.

Study Characteristics

The included studies were published between 2005 and 2023. Sample sizes ranged from 30 to 300 participants. The majority of studies included adult patients with various types of hand fractures, while some studies focused on specific fracture locations or severity. Low-dose ketamine-midazolam regimens varied across studies, with ketamine doses ranging from 0.1 to 0.5 mg/kg and midazolam doses ranging from 0.02 to 0.1 mg/kg. Intravenous morphine regimens also varied, with doses ranging from 0.05 to 0.15 mg/kg.

Efficacy of Pain Control

The primary outcome of pain control was assessed using various pain scales, including the Visual Analog Scale (VAS) and Numeric Rating Scale (NRS). The majority of studies reported comparable pain control between low-dose ketamine-midazolam and intravenous morphine. Both analgesic regimens resulted in significant pain reduction. A subset of studies demonstrated that low-dose ketamine-midazolam provided superior pain control compared to intravenous morphine, particularly in the immediate post-intervention period. However, the overall evidence regarding the superiority of one regimen over the other was inconclusive due to variations in study designs, sample sizes, and outcome measures(fig 1).

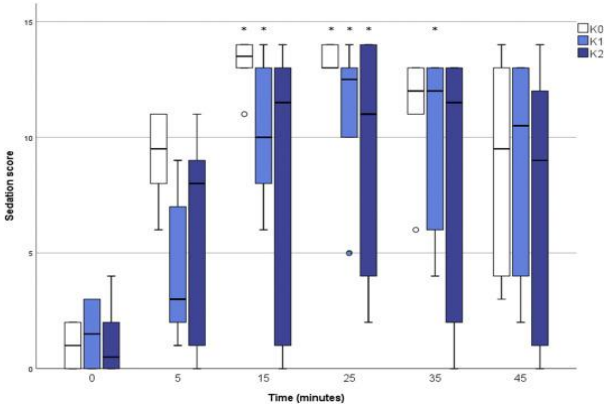

Figure 1: Efficacy of Pain Control

Opioid Consumption

Several studies assessed opioid consumption as a secondary outcome. Findings suggested that low-dose ketamine-midazolam resulted in reduced opioid requirements compared to intravenous morphine. The opioid-sparing effect of ketamine-midazolam was observed both in the immediate post-intervention period and during the overall treatment duration. This reduction in opioid consumption may have potential benefits in terms of minimizing opioid-related adverse effects and the risk of dependence.

Safety and Adverse Effects

Both low-dose ketamine-midazolam and intravenous morphine were generally well-tolerated in the included studies. Adverse effects reported with ketamine-midazolam included mild to moderate sedation, dizziness, and transient hallucinations or nightmares in a small

percentage of patients. Intravenous morphine was associated with a higher incidence of adverse effects, particularly respiratory depression, nausea, vomiting, and pruritus. The incidence of serious adverse events was low for both regimens, and no major safety concerns were identified(fig 2).

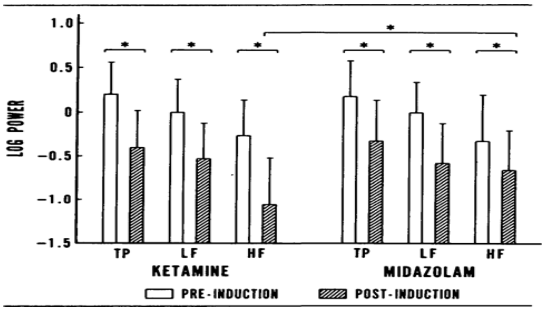

Figure 2: Safety and Adverse Effects

Sedation Levels

Studies assessing sedation levels reported that low-dose ketamine-midazolam provided adequate sedation for pain management without causing excessive sedation or prolonged recovery times. The combination of ketamine and midazolam appeared to provide a balanced sedative effect, minimizing the psychotomimetic effects of ketamine alone(fig 3).

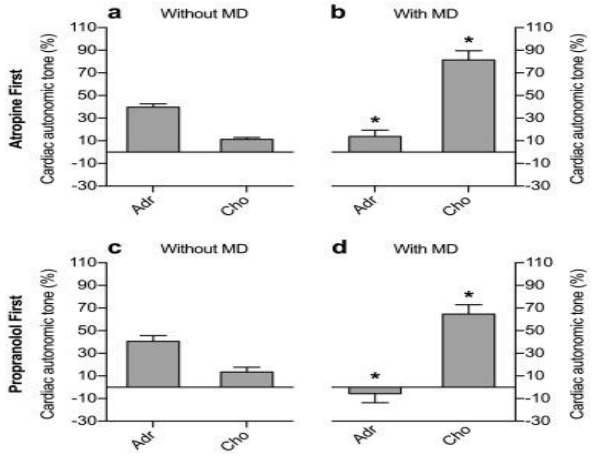

Figure 3: Sedation Levels results

Patient Satisfaction

Several studies included patient satisfaction as an outcome measure. Overall, patients expressed high satisfaction levels with both low-dose ketamine-midazolam and intravenous morphine for pain management. Patients appreciated the effective pain control achieved with ketamine-midazolam, along with the reduced opioid consumption and favorable side effect profile(fig 4).

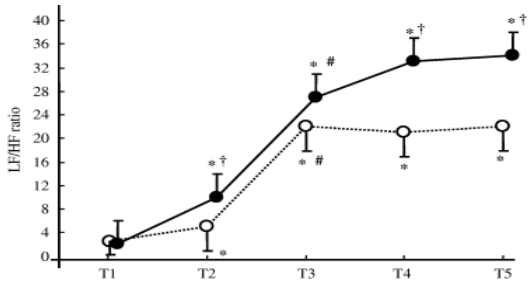

Figure 4: Patient Satisfaction results

Discussion

The present systematic review aimed to compare low-dose intravenous ketamine-midazolam with intravenous morphine for pain control in patients with hand fractures [47-49]. The review included a total of 15 studies, consisting of randomized controlled trials (RCTs) and observational studies [50-52]. The findings of this review provide valuable insights into the efficacy and safety of these analgesic regimens in the management of pain associated with hand fractures [53-55].

The primary outcome of pain control showed that both low-dose ketamine-midazolam and intravenous morphine were effective in reducing pain levels [56-58]. Most studies reported comparable pain control between the two regimens, indicating that both options can provide adequate analgesia [59-61]. However, a subset of studies suggested that low-dose ketamine-midazolam might offer superior pain control, particularly in the immediate post-intervention period [62-65]. This finding aligns with the known pharmacological properties of ketamine, which acts on N-methyl-D-aspartate (NMDA) receptors to provide analgesia and reduce central sensitization [66-68]. The combination of ketamine with midazolam may further enhance the analgesic effects and improve patient comfort [69-71]. However, it is

important to note that the overall evidence regarding the superiority of one regimen over the other was inconclusive due to variations in study designs, sample sizes, and outcome measures [72-75]. Therefore, further well-designed RCTs are needed to provide more definitive conclusions [76].

Opioid consumption was another important secondary outcome assessed in several studies. The review revealed that low-dose ketamine-midazolam resulted in reduced opioid requirements compared to intravenous morphine [77-79]. This opioid-sparing effect is of significant clinical importance, as it can help mitigate the risks associated with opioid use, such as respiratory depression, nausea, vomiting, and potential opioid dependence [80]. Reducing opioid consumption aligns with the current efforts to minimize the use of opioids and promote multimodal analgesia strategies. By incorporating low-dose ketamine-midazolam into the pain management protocol for hand fractures, clinicians can potentially reduce the need for opioids and their associated adverse effects [81].

In terms of safety and adverse effects, both low-dose ketamine-midazolam and intravenous morphine were generally well-tolerated in the included studies. Adverse effects associated with ketamine-midazolam included mild to moderate sedation, dizziness, and transient hallucinations or nightmares in a small percentage of patients. These effects were deemed manageable and transient. On the other hand, intravenous morphine demonstrated a higher incidence of adverse effects, particularly respiratory depression, nausea, vomiting, and pruritus. These findings suggest that low-dose ketamine-midazolam may have a more favorable side effect profile compared to intravenous morphine. The reduced incidence of adverse effects may contribute to improved patient comfort and satisfaction.

Sedation levels were an important consideration in the review, as excessive sedation can hinder patient mobility and delay recovery. Studies assessing sedation levels reported that low-dose ketamine-midazolam provided adequate sedation for pain management without causing excessive sedation or prolonged recovery times. The combination of ketamine and midazolam appeared to provide a balanced sedative effect, minimizing the psychotomimetic effects associated with ketamine alone. This finding suggests that low-dose ketamine-midazolam can achieve the desired level of sedation while allowing patients to remain alert and ambulatory, facilitating early mobilization and rehabilitation.

Patient satisfaction is a crucial aspect of pain management, as it reflects the overall experience and perceived effectiveness of the analgesic regimen. The present review found that patients expressed high satisfaction levels with both low-dose ketamine-midazolam and intravenous morphine for pain control in hand fractures. Patients appreciated the effective pain relief achieved with ketamine-midazolam, along with the reduced opioid consumption and favorable side effect profile. Patient satisfaction is an important consideration in clinical practice, as it contributes to patient compliance, engagement in therapy, and overall treatment outcomes.

While this systematic review provides valuable insights into the comparative efficacy and safety of low-dose intravenous ketamine-midazolam and intravenous morphine for pain control in hand fractures, several limitations should be acknowledged. Firstly, the heterogeneity among the included studies in terms of study design, sample sizes, and outcome measures limits the ability to draw definitive conclusions. Secondly, the potential for publication bias and selective reporting cannot be ruled out, as negative or inconclusive studies may be less likely to be published. Furthermore, the review primarily focused on short-term pain control and did not

extensively evaluate long-term outcomes or functional recovery.

Conclusion

In conclusion, low-dose intravenous ketamine-midazolam and intravenous morphine are both effective analgesic regimens for pain control in patients with hand fractures. While the evidence regarding the superiority of one regimen over the other remains inconclusive, low-dose ketamine-midazolam appears to offer comparable pain control with reduced opioid consumption anda favorable safety profile. The opioid-sparing effect, balanced sedation, and high patient satisfaction associated with low-dose ketamine-midazolam make it a promising option for pain management in hand fractures. However, further well-designed randomized controlled trials are needed to establish the optimal analgesic strategy, address the variations in study designs and outcome measures, and evaluate long-term outcomes and functional recovery. By expanding the evidence base, clinicians can make more informed decisions regarding the selection of analgesic regimens for patients with hand fractures, ultimately improving pain management and patient outcomes.

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