Asian Journal of Medical Principles and Clinical Practice

Volume 6, Issue 2, Page 153-160, 2023; Article no.AJMPCP.100923

Use of Ketamine for Sedation and Analgesia in the Emergency Department Compared to Alternatives: A Systematic Review and Meta Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/100923

Review Article

Received: 04/04/2023
Accepted: 09/06/2023
Published: 21/06/2023

ABSTRACT

To carry out painful treatments in the ED successfully, procedural sedation is required. The two most widely utilised drugs are ketamine and benzodiazepines/opioids, with ketamine offering sufficient analgesia and maintaining airway muscle tone. While benzodiazepines and opioids can

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cause respiratory depression, ketamine is linked to negative side effects. The effectiveness and safety of ketamine and midazolam/fentanyl are contrasted in this study. A database search and a manual search that involved looking through the reference lists of papers that the database search had turned up were both utilized to find research that were pertinent to our issue. Using the Cochrane risk of bias tool in the Review Manager software (Review Manager (RevMan) (Computer programme), a methodological quality analysis of the articles that were eligible for inclusion was done. The Cochrane Collaboration, Version 5.4, 2020).
Additionally, pooled analysis was carried out with the aid of the Review manager programme. Seven of the 1366 papers in the study were chosen for examination. Combined data revealed that the effects of ketamine and midazolam/fentanyl on pain scores during procedures and the depth of sedation assessed by the University of Michigan sedation scale were comparable. The ketamine group, however, had much more deep sedation as measured by the Modified Ramsay Sedation Score. Vomiting and nausea were the only notable side effects, and they were more common in the ketamine group. Our data indicate that ketamine is just as effective for procedural sedation as the combination of midazolam and fentanyl, but it is linked to more side effects. Consequently, midazolam/fentanyl can be suggested for procedural sedation in the emergency department.

Keywords: Systematic review and meta-analysis; emergency department; PSA; procedural sedation and analgesia; ketamine; opioids; benzodiazepines.

1. INTRODUCTION

Procedure sedation is a crucial approach that aids emergency doctors (EPs) in carrying out uncomfortable procedures in the emergency department (ED) quickly and humanely. However, without the right training, monitoring of vital signs, and quality assurance, sedation could lead to major adverse outcomes. In the United Kingdom (UK), a 1995 study by Quine indicated that only 40% of patients received monitoring of their oxygen saturation during the procedure, and that there was an estimated fatality risk of one in every 2000 patients sedated for gastroscopy [1]. Since then, numerous studies have demonstrated that when the current sedation recommendations are followed, procedural sedation is safe and deaths are eliminated [2,3]. a number of substances, including as benzodiazepines, opioids, and ketamine. A special dissociative anaesthetics condition is provided by the phencyclidine derivative ketamine [4].

While favourably maintaining airway muscle tone, airway reflexes, and spontaneous breathing, it typically offers great analgesia and forgetfulness [4,5]. It can be given intravenously (IV) or intramuscularly (IM), among other methods. Fast recovery and avoidance of temporary apnea that is likely to appear during a sudden push are typically made possible by IV injection (1-2 mg/kg over 30–60 seconds).

Contrarily, opioids and benzodiazepines are combined to increase dangers. Midazolam with fentanyl is the most widely used benzodiazepine/opioid combination in procedural sedation. According to a research by Kennedy and colleagues, the combination had a low prevalence of nausea and vomiting (9%) and hypotension (6.2%) but caused total amnesia in 85% of the patients [6]. However, there is a higher risk of respiratory depression with this combo regimen. One of the patients needed positive-pressure breathing, according to Cevik and colleagues, who observed a relatively high prevalence of hypoxia (76.7%) [7]. In comparison to other frequent drug combinations, the midazolam-fentanyl combination has also been linked to increased pain, anxiety, and distress scores [6,7]. To our knowledge, ketamine comparisons to other sedatives and analgesics have not been the subject of a systematic review

2. METHODOLOGY

2.1 Eligibility Criteria

The standards for including and excluding articles from the current review were developed by one reviewer. The following list of inclusion requirements was provided: studies that explicitly contrasted the effectiveness or safety of ketamine with any benzodiazepine and opioid combination. English-language publications of randomised and observational studies. This criterion was crucial since it prevented direct translations of technical words from impairing the scientific investigation of the current study. Additionally, trials in which an emergency

scenario was used to administer procedural sedation. The exclusion criteria, however, were as follows: Studies written as letters to the editor, instructions, abstracts of complete publications, case reports, or systematic reviews. In studies, ketamine and other sedatives were compared to benzodiazepines and opioids.

2.2 Literature Search

A database search and a manual search were both employed as search techniques to find studies that were relevant to our subject. Utilizing specific search criteria, the following electronic databases were searched: PubMed, ScienceDirect, Medline, Google Scholar, and Scopus. The following search criteria were used: (benzodiazepines" AND "Opioids" OR "Benzodiazepines/opioids" OR "fentanyl/ midazolam" OR "fentanyl/diazepam" OR "morphine/midazolam" OR "morphine/ diazepam") AND ("procedural sedation" OR "PSA") AND ("Emergency setting" OR "Emergency department" OR " The manual search, on the other hand, involves looking through the references of studies that were found in the electronic databases to find further research. During the search, we avoided retrieving nearly identical documents as well as gray literature. These papers would have jeopardized our scientific research, thus this specification was crucial for it.

2.3 Quality Assessment

The University of Michigan Sedation Scale (UMSS) and the Modified Ramsay Sedation Score (MRSS) were used in this study to analyze the level of sedation [8,9]. Additionally, oxygen desaturation was seen as a negative event if the patient needed to stop the process and/or receive treatment to get well.

3. RESULTS

We found 1366 articles with the keywords entered in the search strategy using the database search approach. When we looked for duplicates in these articles, we discovered 408 that were either nearly identical or exact copies. The duplicates were eliminated from the study, and from the remaining articles, 622 were eliminated based on the inspection of their papers and abstracts. We were unable to download 281 of the 336 remaining papers because they either contained ongoing trials, abstracts without complete supporting documentation, letters to the editor, guidelines, case reports, or systematic reviews.

Only seven papers were found to be suitable for analysis in this review once the study selection process was complete. The remaining 48 articles were unsuitable for a variety of reasons, including: seven were published in different languages; 39 compared ketamine with other sedatives to a combination of benzodiazepines and opioids; or compared ketamine to individual benzodiazepines or opioids; and two assessed the safety of ketamine and benzodiazepines/ opioids but did not specifically list the various complications associated with each sedative agent. The PRISMA diagram (Fig. 1) shows a list of the criteria for selecting literature.

3.1 Pain Scores

Three studies reported experiencing pain throughout the procedures, and the 11-point NRS was used to quantify it. These studies' combined data revealed that the total pain score did not change.

But the analyses revealed significant heterogeneity, as seen in Fig. 2.

3.2 Sedation Depth

While one study employed the MRSS, two studies used the UMSS to determine the total level of sedation. The mean sedation depth between the groups was comparable, according to data pooled from the two investigations using the UMSS (SMD: 0.28; 95% CI: -0.09 - 0.65; $p = 0.12$). However, as shown in Fig. 3, the results of the study utilising MRSS demonstrated that ketamine provided considerably more deep sedation than the midazolam/fentanyl combination (SMD:0.80; 95% CI: 0.15 - 1.44; $p = 0.02$).

4. DISCUSSION

Patients undergoing unpleasant and anxiety-inducing operations in the ED frequently get procedural sedation as a treatment. There has been extensive research on the effectiveness and safety of various sedation protocols, but little is known about how well ketamine works in comparison to a mix of benzodiazepines and opioids. The main objective of this study was to contrast ketamine with the most widely used benzodiazepine / opioid combination

(midazolam/fentanyl). Our research has demonstrated that ketamine is equally as effective in reducing procedural pain and inducing procedural sedation as midazolam/fentanyl. However, we found that ketamine is substantially more linked to the frequency of vomiting than the combination of midazolam and fentanyl.

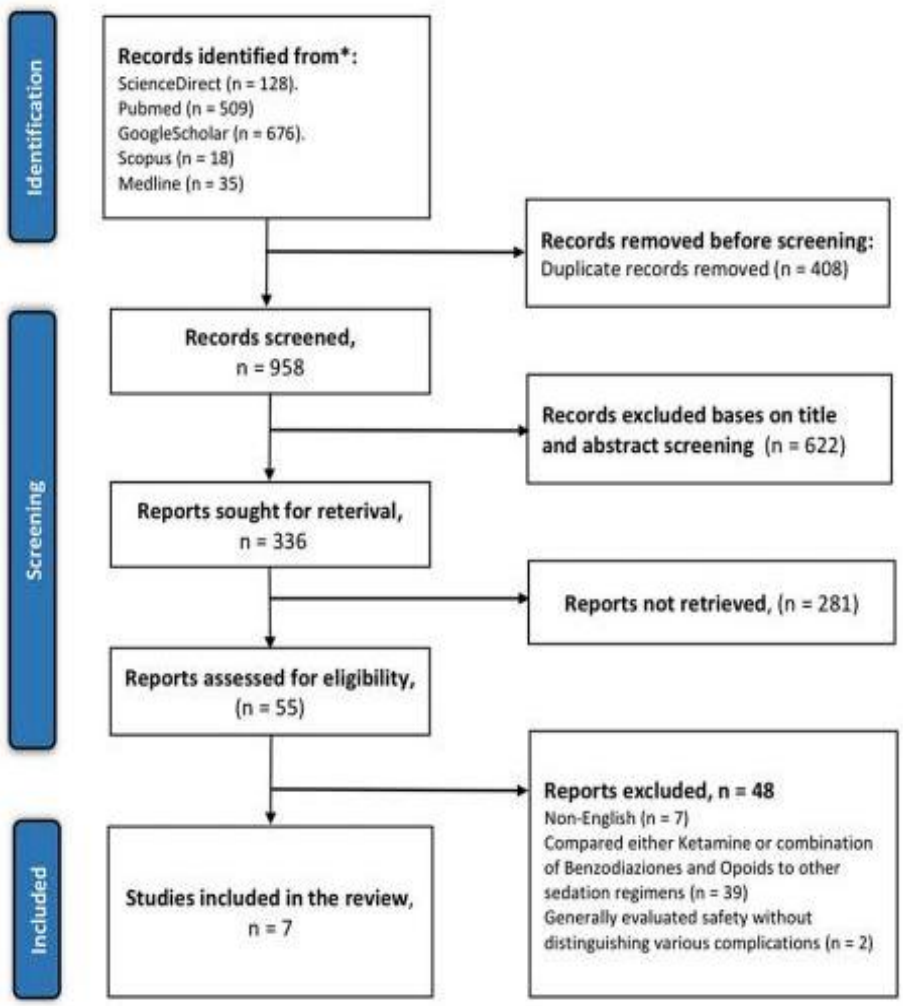

Fig. 1. Identification of studies via database and registers [10]

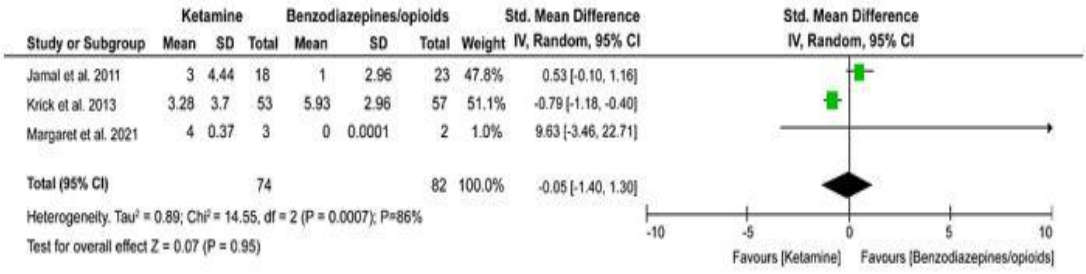

Fig. 2. A Forest plot comparing pain scores during proceduresbetween ketamine and midazolam/fentanyl [10]

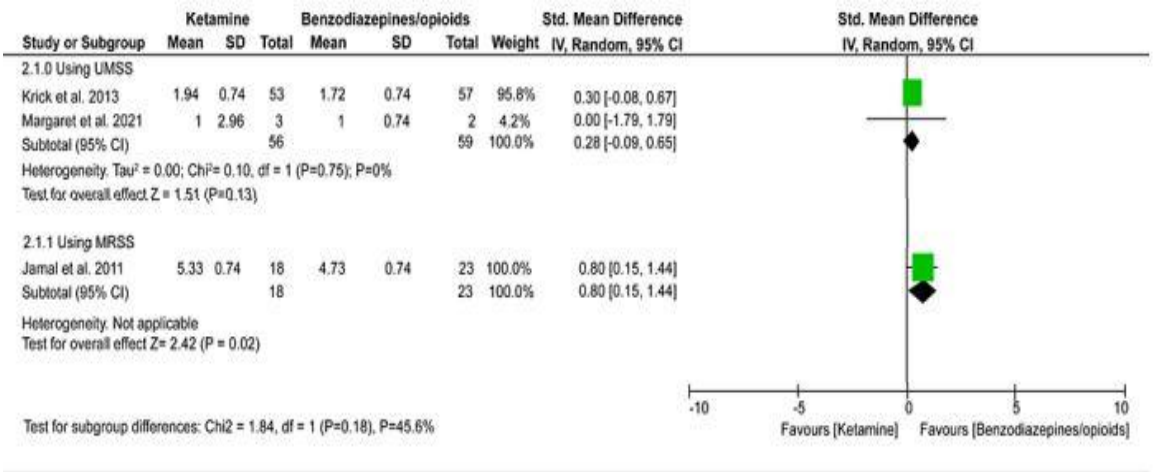

Fig. 3. A Forest plot comparing sedation depth between ketamine and midazolam/fentanyl [10]

Contradictory data have been published in a study involving children having gastrointestinal (GI) endoscopy, despite our meta-analysis results suggesting that ketamine would be beneficial as a midazolam/fentanyl combination in delivering procedural sedation [11]. The Ohio State University Behavioural Scale (OSUBS), which is regarded in earlier research as a trustworthy and valid method for evaluating patients' behavior during dental and GI endoscopic procedures [12,13], was used in that study to assess the efficacy of the sedation regimens. In the study, "effective sedation" was defined as the ability to make patients "quiet, still, and unrestrained," and ketamine was found to be more effective than the midazolam/fentanyl combination in this regard. On the other hand, individuals who were "vocalizing distress, moving, and restrained" were considered to be under ineffective sedation.

It is crucial to remember that this study had a number of restrictions, which could have affected the findings. First off, the study sample size was limited, which gave the findings a bias due to selection. Second, the study adopted a general definition of "moving" and "needing restraint," where movement was classified as either deliberate (combative) or unintentional (drug-induced). The findings of that study cannot be utilized to direct clinical management for procedural sedation due to these limitations. To completely confirm such findings, more randomized trials are necessary.

Comparing the adverse events related to the sedative regimes was the study's other main goal. We discovered that ketamine dramatically raised the likelihood of nausea and vomiting. This result was in line with a recent prospective research of 151 patients, which found that nausea and vomiting were the second most frequent adverse event, occurring at a rate of 28.7% (25/151) after ketamine sedation [14].

Similar to this, a prior study that frequently employed ketamine for procedural sedation noted that nausea and vomiting were the most frequent side effects seen in the patients. The findings of that study indicated that 10 patients experienced adverse effects, six of whom vomited after receiving ketamine for procedural sedation [15]. Additionally, a recent meta-analysis we conducted comparing ketamine alone to ketofol (a combination of ketamine and propofol) revealed that ketamine was strongly linked to worsened nausea and vomiting [16]. However, data suggests that delayed episodes of vomiting and nausea may be seen in patients receiving ketamine, according to McQueen and colleagues. All of these trials reveal incidences of vomiting and nausea during the sedative period.

In contrast, none of the patients who received the combination of midazolam and fentanyl vomited after being discharged. To fully support this finding, additional research examining post-discharge adverse occurrences are needed. The prevalence of laryngospasm is higher in individuals receiving ketamine than in those getting midazolam/fentanyl combined (0.2% vs. 0%, respectively), according to our meta-analysis. Our study's data on laryngospasm prevalence are consistent with prior meta-analyses' findings. Laryngospasm was shown to be 0.26 percent more common in patients receiving ketamine when Green and colleagues combined data from 32 investigations [17].

The prevalence rate seen in both this meta-analysis and our study is modest, indicating that ketamine-related laryngospasm is infrequent, typically transitory, and rapidly responsive to oxygen and assisted ventilation. This conclusion is supported by a research by Lightdale and colleagues, in which one patient who experienced laryngospasm and a 50% oxygen desaturation was treated with positive pressure ventilation and recovered to 100% oxygen saturation and full spontaneous ventilation [11]. Additionally, there is evidence linking ketamine to recurrent laryngospasm in emergency departments. For instance, two paediatric patients who received injectable ketamine for sedation were shown to have repeated bouts of laryngospasm by Cohen and colleagues [18]. A seven-year-old patient taking intravenous ketamine was described in a case report as experiencing recurring laryngospasm.

The second incident, which happened while the patient was being moved on a transport trolley, was treated with PPV and 5 mg of succinylcholine. Three other laryngospasm events followed this one, but no additional episodes were noted. Our research also reveals that the incidence of hypoxemia (oxygen saturation less than 90%) is higher in the midazolam/fentanyl group than in the ketamine group, despite the difference being minor (4% vs. 2.3%, respectively). The fact that these drugs elicit dose-related suppression of the airway protective reflexes and ventilatory drive can be linked to the oxygen desaturation seen in individuals sedated with the midazolam/fentanyl combination.

Because of this, EPs who use these drugs for procedural sedation must be familiar with airway care and knowledgeable about the appropriate reversal agents. It is important to note that in some cases of oxygen desaturation, treatments are not interrupted because measures to correct the situation, such as elevating the jaw and increasing nasal catheter oxygen flow, are taken [19]. Evaluation of the effectiveness of the two sedation regimens also requires consideration of patient or clinician satisfaction, appropriate sedation, and the success of the treatments. On the basis of a Likert scale, a randomised trial contrasting intranasal (IN) ketamine with IN midazolam/fentanyl discovered that doctors were more content with the use of IN midazolam/fentanyl than IN ketamine (100% (4/4)

However, a Canadian study found that only 54% of the 90 parents contacted during the follow-up could respond, and of those who could, they said they were equally satisfied with the procedural sedation given to their children during painful procedures and would pick similar sedation techniques in the future [20]. Furthermore, the study asserted that midazolam/fentanyl was adequate for all 129 individuals but only 95% of those receiving ketamine had acceptable sedation. Similar studies conducted in South Africa showed that ketamine and a drug combination of fentanyl and midazolam efficiently managed pain.

Monitoring alterations in vital signs is also essential for assessing the effectiveness of procedural sedatives. When using ketamine, systolic blood pressure (SBP) increased significantly (from 125 mmHg to 130 mmHg, $p = 0.026$) and diastolic blood pressure (DBP) increased significantly (from 66 mmHg to 74 mmHg, $p = 0.0001$) in a research comparing sedation in patients undergoing uterine evacuation for incomplete miscarriage [21-25].

However, when utilizing a midazolam/fentanyl combination for sedation, the data did not demonstrate any appreciable alteration in either DBP or SBP. The study's findings also showed that the heart rate was not considerably impacted by the sedative regimes. For patients with compensated hemodynamic instability, when the combination of fentanyl and midazolam may cause a breakdown in compensation, the impact of ketamine to elevate SBP and DBP may be beneficial. However, because of this side effect, ketamine should be administered with caution to patients with underlying hypertension problems, particularly those who are more likely to experience cerebrovascular accidents [26-28].

5. CONCLUSIONS

Our findings indicate that for procedural sedation and analgesia in the ED, ketamine alone is just as efficient as a mix of midazolam and fentanyl. However, it has some side effect than the midazolam/fentanyl combination because it is strongly linked to vomiting, nausea, visual hallucinations, and laryngospasm. However, data suggests that ketamine is linked to a considerable rise in SBP and DBP; as a result, it should be administered with caution to patients with hypertension, especially those who are more likely to experience cerebrovascular accidents. We can suggest utilizing the midazolam/fentanyl

combination for procedural sedation in the Emergency Department if we take safety into account.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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