

**Use of ketamine for sedation and analgesia in the emergency department
Compared to alternatives
(Systematic Review and meta analysis)**

Abstract:

Procedural sedation is essential in the ED to conduct painful procedures effectively. Ketamine and benzodiazepines/opioids are commonly used, with ketamine providing adequate analgesia and preserving airway muscle tone. However, ketamine is associated with adverse effects while benzodiazepines/opioids can lead to respiratory depression. This study compares the safety and efficacy of ketamine and midazolam/fentanyl. Two search methods were used to identify studies related to our topic, including a database search and a manual search involving screening reference lists of articles retrieved by the database search. A methodological quality appraisal was conducted on the articles suitable for inclusion using Cochrane's risk of bias tool in the Review Manager software (Review Manager (RevMan) (Computer program). Version 5.4, The Cochrane Collaboration, 2020). Moreover, pooled analysis was performed using the Review manager software. The study analyzed 1366 articles, of which seven were included for analysis. Pooled data showed that ketamine and midazolam/fentanyl had similar effects on pain scores during procedures and sedation depth measured by the University of Michigan sedation scale. However, the Modified Ramsay Sedation Score showed significantly more profound sedation in the ketamine group. The only significant adverse events were vomiting and nausea, which had a higher incidence in the ketamine group. Our data suggest that ketamine is as effective as the midazolam/fentanyl combination for procedural sedation but is associated with higher incidences of adverse events. Therefore, midazolam/fentanyl can be recommended for procedural sedation in the ED. However, it should be provided in the presence of a physician comfortable with airway management due to high incidences of oxygen desaturation.

Keywords: systematic review and meta-analysis, emergency department, psa, procedural sedation and analgesia, ketamine , opioids, benzodiazepines

Introduction

Procedural sedation is a vital technique that helps emergency physicians (EPs) conduct painful procedures humanely and timely in the emergency department (ED). However, sedation might result in serious adverse events without proper training, monitoring of vital signs, and quality assurance. A 1995 study by Quine reported a mortality rate of approximately one in every 2000 patients sedated for gastroscopy in the United Kingdom (UK) and found that only 40% of the patients had monitoring of oxygen saturation during the procedure [1]. Since then, multiple studies have proved that procedural sedation is safe and deaths are eradicated when the current sedation guidelines are adhered to [2,3]. Various agents, including benzodiazepines, opioids, ketamine, nitrous oxide, etomidate, and propofol, have been used for procedural sedation. Ketamine is a phencyclidine derivative that offers a unique dissociative anesthetics state [4]. It usually provides excellent analgesia and amnesia while favorably preserving airway muscle tone, airway reflexes, and spontaneous respiration [4,5]. It can be administered in various ways, including intravenously (IV) and intramuscularly (IM). The IV administration (1-2 mg/kg) over 30-60 seconds usually allows fast recovery and evades transient apnea that is likely to manifest in a rapid push.

On the other hand, opioids are combined with benzodiazepines to accentuate risks. The most popular benzodiazepine/opioids combination in procedural sedation is the combination of midazolam with fentanyl. A study by Kennedy and colleagues showed that the combination resulted in complete amnesia in 85% of the patients and resulted in a low rate of nausea and vomiting (9%) and hypotension (6.2%) [8]. However, this combination regimen is associated with an increased risk of respiratory depression. Cevik and colleagues reported a very high hypoxia incidence (76.7%), requiring positive-pressure ventilation in one of the patients [9]. The midazolam-fentanyl combination has also been associated with higher pain, anxiety, and distress scores than other common drug combinations [8,9]. To our knowledge, no systematic review has been conducted to compare ketamine to a combination of benzodiazepines and opioids in procedural sedation. Therefore, the current study will compare the efficacy and safety of ketamine with the most common benzodiazepine/opioid combination (midazolam/fentanyl) and evaluate which regimen should be considered for procedural sedation.

Methodology

Eligibility Criteria

One reviewer created the criteria to include and exclude articles from the current review. The inclusion criteria were outlined as follows: Studies that directly compared the efficacy or safety of ketamine with any combination of benzodiazepine with opioids. Observational and randomized trials published in English. This criterion was vital since it helped evade direct translations of scientific terms that would otherwise tamper with the scientific research of the present study. And studies in which procedural sedation was provided in an emergency setting. On the other hand, the exclusion criteria were as follows: Studies designed as either letters to the editor, guidelines, abstracts without full articles, systematic reviews, and case reports. Studies compared ketamine combined with other sedatives to a combination of benzodiazepines with opioids or compared ketamine to individual benzodiazepines or opioids. And studies that generally evaluated the safety of ketamine and benzodiazepines/opioids without specifying the various complications associated with each sedation agent.

Literature Search

Two search methods were used to identify studies related to our topic, a database search, and a manual search. The database search involved utilizing a well-defined search strategy on the following electronic databases; PubMed, ScienceDirect, Medline, Google Scholar, and Scopus. This search strategy was as follows; (“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 “Emergency room”). On the other hand, the manual search involved perusing the reference lists of studies identified from the electronic databases for additional studies. We avoided retrieving close or exact duplicates and gray literature during the search. This specification was important for our research because these articles would have undermined our scientific research.

Quality Assessment

For this study, the sedation depth was analyzed using two sedation score scales, including the University of Michigan sedation scale (UMSS) and the Modified Ramsay sedation score (MRSS) [10,11]. In addition, oxygen desaturation was considered an adverse event if patients required termination of the procedure and/or intervention to resolve the condition.

Results

Using the database search method, we attained 1366 articles with the keywords specified in the search strategy. We analyzed these articles to identify duplicates and found that 408 were either close or exact duplicates. The duplicates were excluded from the study, and the remaining articles had their papers and abstracts screened, of which 622 were excluded based on this screening process. Out of the 336 remaining articles, we did not retrieve 281 because they were either ongoing trials, abstracts without full evidence, letters to the editor, guidelines, case reports, or systematic reviews. At the end of the study selection process, we only identified seven articles suitable for analysis in this review. The other 48 articles were unsuitable due to the following reasons; seven were published in different languages, 39 compared ketamine combined with other sedatives to a combination of benzodiazepines with opioids or compared ketamine to individual benzodiazepines or opioids, and two evaluated the safety of ketamine and benzodiazepines/opioids but did not specify the various complications associated with each sedation agents. A summarized literature selection criteria are shown in the PRISMA diagram below (Figure 1)

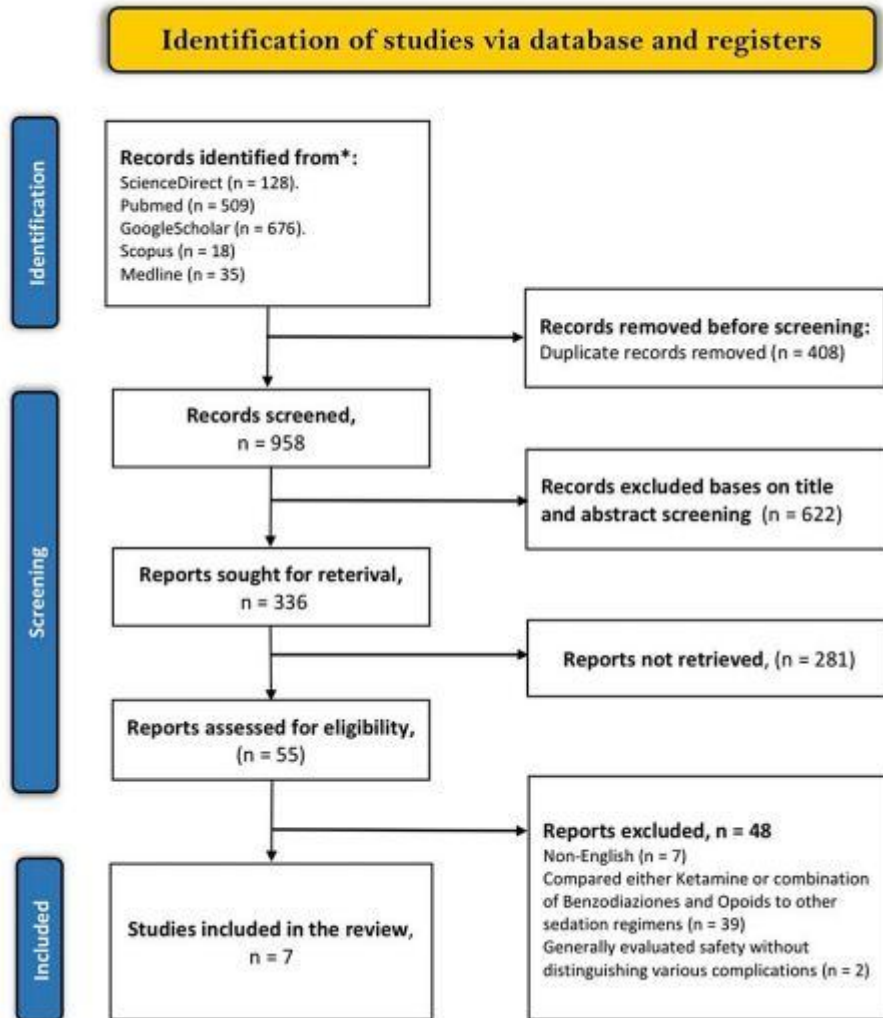
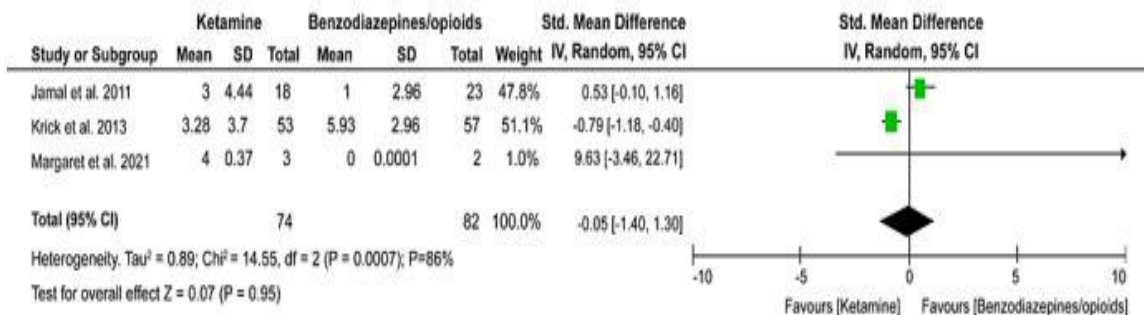


Fig 1

Pain Scores

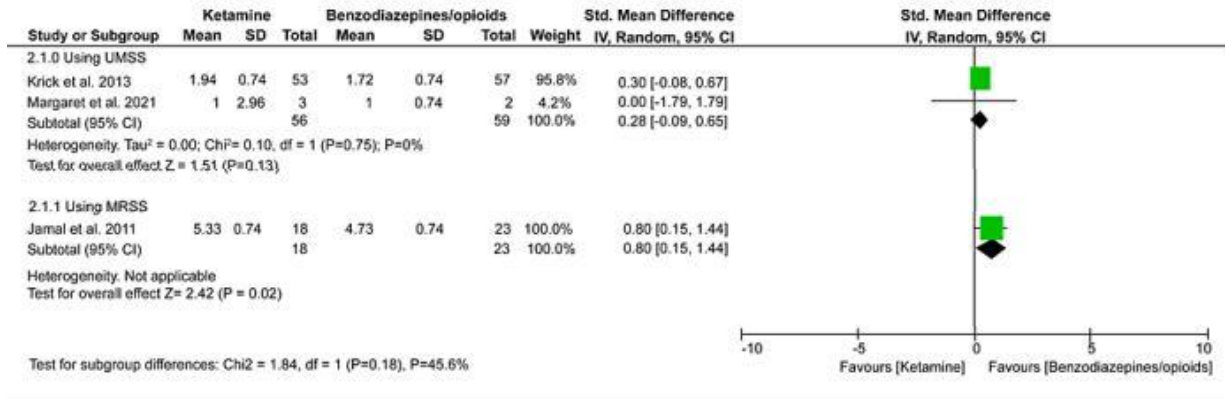
Pain during the procedures was reported in three studies and was measured using the 11-point numerical rating score (NRS). Data pooled from these studies showed that the overall pain score did not differ

However, the analysis showed substantial heterogeneity, as described in Figure 2



Sedation Depth

Two studies calculated the overall sedation depth using the UMSS while one used the MRSS. Data pooled from the two studies using the UMSS showed that the mean sedation depth between the groups was similar (SMD: 0.28; 95% CI: -0.09 - 0.65; p = 0.12). However, data from the study using MRSS showed that ketamine offered significantly more profound sedation than the midazolam/fentanyl combination (SMD:0.80; 95% CI: 0.15 - 1.44; p = 0.02) as described in Figure 3



Discussion

Procedural sedation is a routine treatment for patients enduring painful and anxiety-provoking procedures in the ED. Enormous inquiry on the safety and efficiency of distinct sedation regimens has been carried out; nonetheless, little is understood about the efficacy of ketamine compared to a combination of benzodiazepines and opioids. Therefore, the primary aim of this study was to compare ketamine with the most common benzodiazepine/opioid combination (midazolam/fentanyl). Our study has shown that ketamine is as effective as midazolam/fentanyl in alleviating procedural pain and providing procedural sedation. However, we noticed that ketamine is significantly

associated with the prevalence of vomiting than the midazolam/fentanyl combination. Although our meta-analysis results suggest that ketamine might be effective as a midazolam/fentanyl combination in providing procedural sedation, contradictory evidence has been reported in a study involving children undergoing gastrointestinal (GI) endoscopy [16]. In that study, the effectiveness of the sedation regimens was carried out using the Ohio State University Behavioral Scale (OSUBS) which is considered in other studies as a reliable and valid method for evaluating patients' behavior during dental and GI endoscopy procedures [19,20]. The study described effective sedation as patients rendered "quiet, still and unrestrained," of which ketamine was considered more effective than the midazolam/fentanyl combination. On the other hand, ineffective sedation was described as patients who were "vocalizing distress, moving and restrained." However, it is important to note that this study was subject to various limitations that might have influenced its results. First, the study sample size was small, introducing a selection bias to the study results. Second, the study used a broad definition for "moving" and "needing restraint," of which movement was defined as either intentional (combative) or unintentional (drug-induced). Based on these limitations, the conclusions made in that study cannot be used to guide clinical care in procedural sedation. More randomized trials are required to establish those results fully.

The other primary aim of this study was to compare the adverse events associated with the sedation regimens. We found that ketamine was significantly associated with an increased risk of vomiting and nausea. This finding was consistent with a recent prospective study of 151 patients, which reported that vomiting and nausea was the second most common adverse event occurring at a rate of 28.7% (25/151) after sedation with ketamine [21]. Similarly, a previous study that commonly used ketamine for procedural sedation reported that vomiting and nausea were the most common adverse events observed in the patients. According to the results presented in that study, adverse events were witnessed in 10 patients, of which six out of the nine patients that received ketamine for procedural sedation vomited [22]. Furthermore, our recent meta-analysis comparing ketofol (a combination of ketamine and propofol) to ketamine alone showed that ketamine was significantly associated with increased nausea and vomiting [23]. All these studies report incidences of vomiting and nausea during the sedation period; however, evidence shows that delayed cases of vomiting and nausea might be observed in patients receiving ketamine, according to McQueen and colleagues. Post-discharge vomiting was recorded in 110 patients that had received ketamine as the agent for procedural sedation. In contrast, none of the patients receiving the midazolam/fentanyl combination had post-discharge vomiting. However, more studies evaluating postdischarge adverse events are required to establish this finding fully. Our meta-analysis has also confirmed that the prevalence of laryngospasm is higher for patients receiving ketamine than the midazolam/fentanyl combination (0.2%

vs. 0%, respectively). The prevalence of laryngospasm recorded in our study aligns with that reported in previous meta-analyses. Green and colleagues pooled data from 32 studies evaluating laryngospasm in patients receiving ketamine and found a prevalence of 0.26% [7]. The prevalence rate recorded in this meta-analysis and ours is low, suggesting that laryngospasm related to ketamine is relatively uncommon and is usually transient and responds quickly to oxygen and assisted ventilation. This finding is evident in a study by Lightdale and colleagues where one patient who developed a case of laryngospasm and an oxygen desaturation of 50% was intervened using positive pressure ventilation and returned to full spontaneous ventilation and oxygen saturation of 100% [16]. Evidence also suggests ketamine can be associated with recurrent laryngospasm in the ED. For example, Cohen and colleagues reported recurrent episodes of laryngospasm in two pediatric patients who received intramuscular ketamine for sedation [24]. Additionally, a case report of a seven-year-old patient receiving intravenous ketamine reported recurrent episodes of laryngospasm [25]. According to this case report, the first episode of laryngospasm occurred even before the procedure, and it was quickly reversed using positive pressure ventilation (PPV). The second episode occurred when the patient was shifted on a transport trolley and was resolved using 5 mg of succinylcholine and PPV. After this episode, three other episodes of laryngospasm happened, and no other episode was recorded. Our analysis also shows that even though the difference is insignificant, the incidence of hypoxemia (oxygen saturation less than 90%) is higher in the midazolam/fentanyl group than in the ketamine group (4% vs. 2.3%, respectively). The oxygen desaturation observed in patients sedated with the midazolam/fentanyl combination can be attributed to the fact that these agents cause dose-related suppression of the airway protective reflexes and ventilatory drive. Therefore, EPs using these agents for procedural sedation must be comfortable with airway management and well-informed on the pertinent reversal agents. However, it is worth noting that in some of the oxygen desaturation events, the procedures are not suspended since actions such as elevation of the jaw and nasal catheter oxygen flow are carried out to reverse the condition [26]. Patient or clinician satisfaction, adequate sedation, and the success of the procedures are also crucial in assessing the efficacy of the two sedation regimens. A randomized trial that compared intranasal (IN) ketamine with IN midazolam/fentanyl analyzed the satisfaction of nurses and physicians based on the Likert scale and found that the clinicians were more satisfied with the use of IN midazolam/fentanyl than IN ketamine (100% (4/4) vs. 16.7% (1/6), respectively) [18]. However, a Canadian study showed that of the 90 parents reached during the follow-up, 54% were able to provide their response, of which they responded that they were equally satisfied with the procedural sedation provided to their children during painful procedures and would choose similar sedation techniques in the future [15]. Furthermore, the study claimed that 95% of 129 patients receiving ketamine had adequate sedation while midazolam/fentanyl was sufficient for all patients.

Similarly, South African research revealed that ketamine and combining fentanyl and midazolam effectively provided appropriate pain management.

Monitoring changes in vital signs is also crucial in evaluating the efficacy of procedural sedation agents. A study comparing sedation in patients undergoing uterine evacuation for incomplete miscarriage reported a significant rise in systolic blood pressure (SBP) (from 125 mmHg to 130 mmHg, $p = 0.026$) and diastolic blood pressure (DBP) (from 66 mmHg to 74 mmHg, $p = 0.0001$) when using ketamine [17]. However, the data did not show any significant change in either DBP or SBP when using a midazolam/fentanyl combination for sedation. The study results also revealed that the sedation regimens did not significantly affect the heart rate. This effect of ketamine to increase SBP and DBP may be advantageous for patients with compensated hemodynamic instability, where a combination of fentanyl and midazolam may result in a breakdown in compensation. However, this effect also means that ketamine should be used sparingly in patients with underlying hypertensive disorders, especially those at a higher risk of cerebrovascular events.

Conclusions

Our data suggest that ketamine alone is as effective as a combination of midazolam and fentanyl in providing procedural sedation and analgesia in the ED. However, it is highly associated with vomiting, nausea, visual hallucination, and laryngospasm, meaning it is less safe than the midazolam/fentanyl combination. Nevertheless, evidence shows that ketamine is associated with a significant increase in SBP and DBP; thus, it should be used sparingly in patients exhibiting hypertensive disorder, especially those at a higher risk of cerebrovascular events. If we consider safety, we can recommend using the midazolam/fentanyl combination for procedural sedation in the ED. However, a physician comfortable with airway management should provide this sedation regimen due to high incidences of oxygen desaturation.

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