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Review Article

Use of Ketamine, Propofol and their combination (Ketofol) for Procedural Sedation in Emergency Department: A Review

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ABSTRACT

For Procedural Sedation, sedative and Analgesic agents are frequently used in Emergency Department but titration of anesthetic doses should be performed with care, and patients should be continuously monitored. The use of Ketamine, Propofol and their combination (Ketofol) is in common practice, but there is currently no intravenous anesthetic agent that is ideal. Therefore, this review was conducted to analyze the efficacy as well as the potential side effects of these anesthetic agents during procedural sedation. For this purpose, Medline, EMBASE, CCRCT and CINAHL were searched and systematically analyzed and the meta-analysis included all English-language randomized control trials (RCTs) comparing K-P vs propofol for procedural sedation in ED. The study included the data of ED patients who received procedural sedation for non-elective unpleasant procedures. As a result of the removal of duplicate citations and studies that did not fulfill eligibility requirements, a total of 06 RCTs involving 932 patients (412 in the propofol group and 520 in the K-P group). Very high levels of inter-rater reliability (j = 0.88; 95% CI = 0.68 to 1.0) were found in the final selection of included trials, with 95.2% agreement. Data revealed that the combination of Ketamine with propofol was the most effective anesthetic combination in the larger randomized, prospective studies carried out in the ED that had sufficient power to use the maintenance of vital signs and the success of the procedure as endpoints are still required.

INTRODUCTION

Patients seek medical attention in the emergency room (ER) often because of distress. Ketamine has been used for procedural sedation in the emergency room for decades, and its unique analgesic properties have recently garnered interest as a viable alternative to opioids. Because of its dissociative effects, ketamine is also used to calm down anxious patients. These novel applications of ketamine in the ER are the focus of this narrative review. In case of chest injuries or myocardial infarction, for instance, morphine sulfate, titrated to the clinical response and preceded by an antiemetic, is typically beneficial for uncomplicated analgesia. Ketamine is a safe and effective alternative to opioid analgesics for patients with numerous injuries or those who need to undergo manipulation and splint age of fractures, as well as for entrapments and difficult extractions [1, 2]. Most emergency room procedures that need sedation include alleviating pain. Over-sedation may occur if the pain trigger is removed before the medicine has taken its full effect. With its short on- and off-time, propofol appears like a promising medication for this purpose. However, there is a history of reports of a small therapeutic window, which might increase the possibility of profound sedation. Sedative-hypnotic propofol (2, 6-di-isopropyl phenol) has a relatively

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brief duration of action. It is believed to function by increasing the affinity of C-amino butyric acid for its CNS receptors. It lacks pain-relieving capabilities and hence requires additional medication. When compared to benzodiazepines, studies have shown varying degrees of amnesic effects. However, it has well-known euphoric and antiemetic properties [3]. Physicians who work in emergency rooms need to be at ease and competent in administering Procedures for Sedation and Analgesia (PSA). PSA aims to provide a suitable amount of sedation while decreasing pain and anxiety, increasing forgetfulness, decreasing the risk of adverse drug-related events, regulating behavior, and keeping the patient's heart rate and breathing rate steady. The perfect pharmacologic agent for PSA would have rapid start and offset times, be safe across all age groups, be cost-effective and be equally effective through all routes of administration. There is currently no medication that has all of these desirable characteristics; thus, doctors must use therapeutic combinations at variable doses to get the best potential results. In the most recent literature, a PSA combination of low-dose ketamine and propofol (ketofol) has been reported. In this study, we'll try to outline the purported advantages of combining these two drugs, as well as analyze whether or not these are safe and effective [4]. This study aimed to compare propofol, ketamine, and ketofol for procedural sedation in the emergency department, to provide an overview of the current evidence on the safety and efficacy of these medications for this specific use. The study systematically reviewed and analyzed the literature, including randomized controlled trials, observational studies, and case reports. The key outcomes such as onset and duration of sedation, recovery time, adverse events, and patient satisfaction, were focused on the goal to provide a comprehensive and unbiased evaluation of the available evidence and to make recommendations for best practices based on the findings. Medline, EMBASE, CCRCT, and CINAHL, were searched and the meta-analysis included all English-language randomized control trials, comparing K-P vs propofol alone for PSA in the ED.

Characteristics of Ketamine

Ketamine, a phencyclidine derivative, is widely used for procedural sedation, especially in the emergency room, where painful operations are done. When compared to traditional general anesthetics, ketamine produces a unique state of consciousness known as "dissociative anesthesia" due to a separation of the brain's cortex and limbic regions. Increases in its usage and popularity as a sedative agent, especially among children, may be attributed to the drug's relative cardiovascular stability and preservation of protective airway reflexes [1, 5]. In contrast to its forerunner phencyclidine, the anesthetic ketamine was created in the 1960s to be safer and more predictable. Superior amnesia and analgesia are provided, as well as the maintenance of protective airway reflexes and spontaneous breathing without loss of muscle tone. Some doctors are wary of using ketamine alone despite its clear benefits over other medicines because of the drug's potential to generate vivid and scary emergent responses. When delivered at sedative dosages, other notable side effects include sympathomimetic effects and vomiting [5].

Characteristics of Propofol

It was revealed that procedure sedation in the emergency department for necessary painful disorders, and propofol provided the baseline for anesthesia. But it was accompanied by over-sedation with the removal of painful stimulus from the patient before the medicine has fully taken action. Due to its short on and off times, propofol was a useful medication in this setting. The danger of progressing to severe sedation, however, has been associated with a limited therapeutic index [6]. The studies showed that it is believed to function by increasing the affinity of c-amino butyric acid for its CNS receptors. It lacks pain-relieving capabilities and hence requires additional medication. When compared to benzodiazepines, studies have shown varying degrees of amnesic effects. Nevertheless, it is known to have euphoric and anti-nausea properties. A single arm's circulation to the brain initiates effects within sixty seconds. The quick redistribution from central nervous system tissue to muscle and fat reduces the duration of action to around 10 minutes, despite a half-life of 13-44 hours [7, 8].

Characteristics of Ketofol

Effective procedural sedation and analgesia for unpleasant operations in the ED may be provided by ketofol because it has reduced the side effects of either medicine. It has been shown that combining propofol with ketamine improves hemodynamic stability, eliminates respiratory depression, provides effective postoperative analgesia and speeds up recovery. The contents of both syringes may be combined in a single bolus and given to the patient at once, or the two can be used separately. For lengthier operations, it may be given as a continuous infusion instead of a bolus [9]. In previous studies, various ratios of ketamine to propofol have been examined. It is yet to be determined what the ideal ratio of ketamine to propofol is, or what the best dosage of the two drugs is. In this brief overview, we focused on the emerging evidence that demonstrated the therapeutic value of combining Ketamine with Propofol [10]. The combination of strong hemodynamic stability, no respiratory depression, rapid recovery, and effective post-procedural analgesia were achieved using a combination

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regimen and consequently, the Ketofol revealed that it might be a great option for combined sedation during medical procedures [4, 11]. We manually reviewed the collected papers' reference lists for additional relevant citations. Trials that could have been appropriate were identified by an independent screening of the search results, and their entire texts were then downloaded and evaluated for inclusion (Table 1).

Author	Drug Name	No of patients	Type of Study	Measured Outcomes	Weakness
(Dikti et al., 2022)	Ketamine	243 Patients in emergency and 215 treated individually	Convenience sampling retrospective, descriptive research	Sedation/recovery time, the frequency of undesirable outcomes	Not controlling the small numbers
(Symington and Thakore, 2021)	Propofol	The number of patients in this study was 82	Analytical description of a retrospective sample of patients	The length of time needed to make a full recovery, the frequency of undesirable outcomes.	Cannot measure the depth of sedation
(Andolfatto *et al.*, 2022)	Ketofol	The total number of patients treated with ketofol was 114	In-depth analysis of past case notes	Having better recovery time than ketamine and Propofol.	No measure of the depth of sedation

Table 1: Comparison of Ketamine, Propofol and Ketofol

Two reviewers utilized a standardized form to gather patients' demographics, sample sizes, painful procedures, pharmacologic drugs, and results. Quality evaluation disagreements were settled by consensus. Review Manager 5.2.4 merged the assessments. Risk ratios (RR) and 95% confidence intervals were used to summarize unfavorable respiratory and total events, and random-effects models were adjusted for heterogeneity (CIs). K-P was more effective than propofol alone for procedural sedation if the RR was less than 1. P<0.05 or a non-1 95% CI for the RR showed statistical significance. No meta-analysis was feasible, thus descriptive data were utilized for sedation, procedure, and recovery periods. I2 assesses the percentage of variance in impact estimates that may be attributable to methodological variation versus a random variation. Variation is high when I2 is below 50%. Prior subgroup analyses comparing juvenile vs. adult patients, ASA physical category, 15 procedures, and study drug dosage were aimed to explain observed discrepancies. Rate criteria were used to grade every outcome's evidence and recommendation strength (Figure 1). A total of 1,688 citations were found that could be useful based on the search terms used. As a result of the removal of duplicate citations and studies that did not fulfill eligibility requirements, a total of 21 full-text publications were obtained for further examination. After excluding 15 papers, this evaluation included 6 RCTs that involved 932 patients (412 in the propofol group and 520 in the K-P group). Very high levels of inter-rater reliability (j = 0.88; 95% CI = 0.68 to 1.0) were found in the final selection of included trials, with 95.2% agreement. We summarize key features of the included studies. Solely two of the studies used only adult participants, while the other two included both adults and children (with one study excluding those younger than 14 and the other including those younger than). The patient group in one experiment was not specified, comprised of children and adolescents between the ages of 3 and 18. 22 Orthopedic procedures accounted for more than 65% of all procedures, whereas abscess drainage accounted for more than 20%.

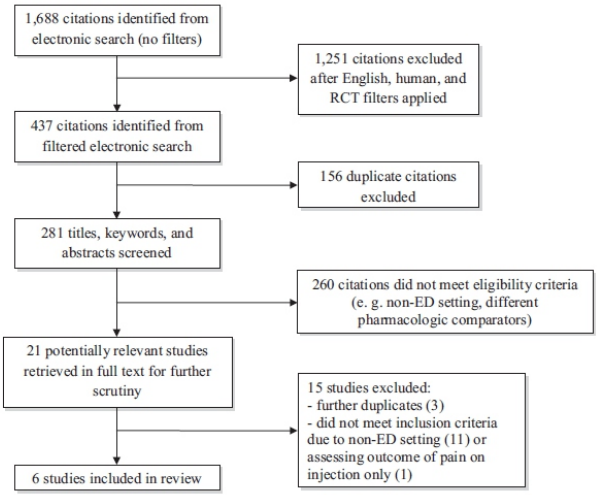

Figure 1: Flow diagram of included studies

Study evidence of Ketamine

A comprehensive six (06) studies were conducted in the literature to analyze the evidence of ketamine. The number of patients who were sedated over the period beginning in September 2020 and ending in March 2021 was 243. And also 215 individuals were treated with ketamine in the emergency department. Both inhalational and intravenous sedative methods (other than ketamine) were disregarded for this investigation. Nitrous oxide, either alone (n=9) or in combination with other methods (n=9), was the second most prevalent procedure, behind ketamine. The age of four years was the most common representation of the patient population (range 14 months to 15 years). One hundred thirty-seven (63.7%) of the patients receiving ketamine sedation were male. Wound care (n=131) and fracture, dislocation, or both care (n=62) were the most prevalent indications for ketamine sedation. The most common starting dosage was 1.25 mg/kg intravenously or 3.94 mg/kg intramuscularly. Seventy individuals needed further doses; 34.8% of those given an intravenous dosage

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and 17.9% of those given an intramuscular dose. Whether it was due to a lengthy operation time (n=32) or insufficient sedation (n=38), additional doses were administered in each case. When comparing the first dosages given intravenously (P=0.07) with intramuscularly (P=0.20), no significant difference was seen between the two groups of individuals needing further sedation.

Study evidence of Propofol

This study evidence analyzed the meaningful use of propofol for the use of procedural sedation in the emergency rooms from an observational, prospective standpoint. Between June 1, 2020, and January 31, 2021, one research investigator enlisted a convenience sample of eligible, consenting patients. The study's investigator was the deciding factor in selecting the convenience sample. The study's investigator was a senior anesthesia resident with emergency medicine residency experience and a board of certification from the American Board of Emergency Medicine. Eighty-two patients were included in the trial during its 6-month duration. They had a mean age of 38 (SD = 14; range = 18-81) and were almost half men. Most of the time incision and drainage (49%) and joint reduction (29%) were the most common indications for EDPS, followed by fracture treatment (11%). Out of the 82 participants, 17 (21%; 95% CI 12%-29%) encountered one of the 28 sedative events; clinical hypoventilation was the most prevalent. Eight respondents had no events, and seven experienced.

Study evidence of Ketofol

This retrospective, observational research examined how often emergency departments utilize propofol for procedural sedation. In the last six months between April 2021 and October 2021 a total of 114 cases, ketofol was used for sedation and pain relief during an emergency, the majority of which were orthopedic, and medication was given at a median dosage of 0.75 mg/kg (range, 0.2 to 2.05 mg/kg for both propofol and ketamine; IQR, 0.6 to 1.0 mg/kg). One hundred and ten patients (96.5%) had their procedures completed without the use of any supplemental sedatives. Doctors, nurses, and patients all gave a median rating of 10 on a scale from 1 to 10 for their overall satisfaction.

Combination of Ketamine and Propofol

The result of Ketamine based on our findings, 76.7% of patients were sent home after recovering under observation in the emergency room, the pediatric assessment unit, or the pediatric ward. The paradoxical agitation of a single patient was the reason for a failed sedative attempt that necessitated a switch to a general anesthetic. Those patients who were first treated for their injuries while sedated afterward required admission for final care. As a result, 165 fewer patients required a general anesthetic, which was a huge relief for the operating room and anesthesia staff. Other benefits include less time spent waiting to be admitted and less interruption to the family's routine. Results of Propofol Based on the data we have at present, it seems that propofol can be administered successfully and safely in the ED. While there is some data available, it seems to be from trials in which participants were under profound sedation or even general anesthesia. Patients may not be fasting or properly prepared for the surgery and even some physicians are not even ready or comfortable to manage the airway instantly, hence it is not advised that non-anesthetists provide these degrees of sedation. Hence, Ketamine combined with Propofol is the most effective anesthetic combination in the available research. Even though all but one of the published studies that were looked at for this article concluded that the combination of Ketamine and Propofol in bolus form provides safer and more effective sedation, larger randomized, prospective studies carried out in the emergency department that had sufficient power to use the maintenance of vital signs and the success of the procedure as endpoints are still required. The reviewed literature suggests that treating PSA with Ketofol in the ER is a safe and effective option. There is some evidence that Ketofol is more effective than either medication alone or as part of combination therapy, however, the evaluated trials are too small, side effects are seldom reported, and the single research performed in the ED is not a randomized controlled trial to make any firm conclusions. Emergency room visits climbed by almost 30% over time. Therefore, it may come as a surprise that the number of pediatric ketamine sedations fell by an average of 10.9% each year. This service may get more difficult to provide when emergency departments face rising demands. Traditional definitions and sedation scales may not apply to ketamine because of the drug's unique mechanism, therapeutic effects and safety profile. Additionally, due to the absence of a well-defined dose-response continuum, dissociative sedation is now defined as the attainment of extreme analgesia and forgetfulness while maintaining protective airway reflexes, spontaneous respirations and cardiac stability. Patients who were apneic after needing just minimal airway manipulation may have been under general anesthesia according to this classification. Propofol has a remarkable safety profile, as shown by the aforementioned observational studies. For instance, Daele *et al.*, followed a large group of people for two years and found no evidence of serious morbidity [12]. Nonetheless, without a comparison group, it cannot be assessed whether the positive results were due to the drug's effects or to better sedation techniques. Minor events, such as temporary hypoxia, occurred at a high incidence, although this may

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reflect the seemingly deep doses of sedation utilized and is comparable to rates previously described with midazolam in a pediatric ED setting. Tolerance of painful stimuli without protest is described as "deep sedation" or "global anesthesia" [10]. For certain procedures, dealing with a pediatric population may need this. There were no cases of aspiration, however, patients were not always instructed to fast before undergoing urgent treatments [13]. For decades, anesthesiologists have benefited from combining ketamine with propofol, but the practice has only just started to expand to other medical specialties. There is a dearth of information in the scientific literature on the bolus administration of ketofol for PSA since its usage is novel to most practitioners [14]. Due to their limited sample size, the existing studies cannot reliably identify differences between groups on any of their predefined outcomes. However, few trials examine the occurrence of other adverse events, such as emerging responses, which may induce practitioners to detour away from Ketofol and adopt another regimen that is determined to be similarly effective if they occur. Furthermore, diverse dosage regimens are utilized in the examined literature, making it challenging to compare and contrast the findings of various research [15-20]. Ketamine is known to retain respiratory function; therefore, it was hypothesized that the combination of ketamine and propofol may counteract the respiratory depression caused by propofol sedation. This possible protective effect is hypothesized to be based on the ability to achieve the desired sedation depth with a lower dose of propofol when using the combination than would otherwise be required if propofol were used alone. Rapid intravenous infusion of ketamine is known to have the potential to cause apnea. In a comparison of ketamine and propofol for mild sedation, a greater proportion of people receiving ketamine alone had symptoms of subclinical respiratory depression. However, this result may have been influenced by the fact that propofol patients utilized supplemental oxygen more frequently than ketamine patients [21-26]. We found that both ketofol and propofol reliably induce profound sedation. Despite the different mechanisms of action of the two medications, the duration and number of doses necessary to induce profound drowsiness were comparable. Deep drowsiness can be produced with 1 to 2 mg/kg of propofol alone, whereas dissociative dissociation with ketamine monotherapy typically needs 1.0 to 1.5 mg/kg. In our investigation, deep sedation with ketofol was reliably accomplished with nearly half of the required dose (0.7 mg/kg; interquartile range [IQR]: 0.55 to 0.90 mg/kg), which is consistent with earlier reports of ketofol use in adults[27-31].

CONCLUSIONS

It was concluded that Ketofol was the preferred agent for numerous procedures. The combination of Propofol and Ketamine is advantageous due to its hemodynamic stability, lack of respiratory depression, rapid recovery, and potent postoperative analgesia. As a sedoanalgesic, the safety and efficacy of Ketofol depend on the dose and ratio of the mixture. Consequently, Ketofol should be an ideal combination medication for procedural sedation. It had fewer adverse respiratory effects than Propofol alone in ED procedural sedation.

Conflicts of Interest

The authors declare no conflict of interest.

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