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Article Review

EXPLORING EFFICACY OF KETAMINE COMBINATIONS: META ANALYSIS & REVIEW OF ITS USE IN SEDATION PROCEDURE

Yudha Ferriansyah[1], Bekti Setiadi[2]
[1]Medical Doctor, Faculty of Medicine Yarsi University, Jakarta, Indonesia
[2]Anesthesiologist, Faculty of Medicine University of Indonesia, Jakarta, Indonesia
*E-mail: yudhaferriansyah@gmail.com

Abstract

Background

Recently, there has been a shift in the philosophy regarding procedural sedation. The best sedation agent should have quick induction and recovery times with few side effects. Several studies have investigated the combination of Ketamine-Dexmedetomidine and Ketamine-Propofol for reducing potential negative side effects during sedation procedures.

Methods

The literature search was performed in PubMed, Medline, Cochrane and Google Scholar with the keywords Sedation Procedure, Ketamine Combination Propofol and Ketamine Combination Dexmedetomidine from 2006 to 2022. We used PICO model which follows the inclusion criteria and PRISMA methods. All variables and data were pooled in Excel, SPSS version 26 and Cochrane.

Results

Total of 372 patients were in Ketamine-Dexmedetomidine group and 373 patients were in Ketamine-Propofol group. Patient characteristics in this study had a mean age of 2.4 to 9.1±1.6 years and mean weight 12 to 23.6±6 kg in the pediatric population and 27 to 51±8.5 years and 75 to 84.5±4.2 kg in the adult population. ASA criteria for each patient are ASA I-IV and the most ASA criteria in patients is ASA II. The procedure time from 5.7 to 63.4 ± 5.3 minutes and also comorbidities.

Conclusion

The combination of drugs in sedation procedures is the best choice to achieve a balanced effect in reducing negative side effects of drugs. Dexmedetomidine-Ketamine appears to be superior than Propofol-Ketamine in terms of hemodynamic stability, oxygen saturation and fewer adverse events. Eventhough Dexmedetomidine-Ketamine has longer recovery time and lower heart rate.

Keywords: Ketamine Combination; Sedation Procedural; Drug Combination

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INTRODUCTION

Propofol is a hypnotic and provides rapid onset and complete recovery from anesthesia (David & Shipp, 2011). It is commonly used during brief surgical interventions. However, it has not an analgesic effect. The use of high-dose Propofol may cause severe complications, such as hypotension, respiratory depression and bradycardia (Phillips et al., 2010). Combining propofol with opioids or ketamine is recommended for improving the quality of sedation and analgesia and minimizing the potential adverse effects of drug-related events, and maintaining a stable cardiovascular and respiratory status (David & Shipp, 2011; Phillips et al., 2010)

Dexmedetomidine, an ultra-selective α2 agonist, has anxiolytic, analgesic, amnestic and sedative properties with no risk of respiratory depression (Carollo et al., 2008). It can effectively reduce the hemodynamic and psychomimetic actions of ketamine (Gupta et al., 2011). Dexmedetomidine has a sympatholytic effect which causes a reduction of heart rate and blood pressure, which can be countered by the sympathomimetic effect of ketamine (Paris & Tonner, 2005; Levanen J et al., 1995).

The best sedation agent should have quick induction and recovery times with few side effects. There is no single agent which completely meets all of these requirements. As a result, different drugs are combined to provide the best sedation with the fewest side effects (Tolia V & Peters JM, 2000). Several studies have investigated the combination of Ketamine-Dexmedetomidine and Ketamine-Propofol for maintaining hemodynamic stability and reducing potential side effects of each drug during sedation and reported that Ketamine-Dexmedetomidine combination led to lower recovery time than Ketamine-Propofol combination (Canpolat et al., 2012; Jiang et al., 2015; fei Gao et al., 2022).

Several depths of sedation assessment methods are used in clinical practice and in research protocols; these include the ASA Continuum of Sedation, the Modified Observer's Assessment of Alertness/Sedation Scale (MOASS), and the Ramsay Sedation Scale (RSS) (American Society of Anesthesiologists, 2019; Coetzee JF, 2010; Gill et al., 2003; Hinkelbein et al., 2018). A previous systematic review focused on sedation (mainly limited to midazolam and propofol) and Dexmedetomidine - Ketamine combination on the quality of sedation/ analgesia, hemodynamic parameters, and recovery time in painful procedures (Li et al., 2018; Chun et al., 2016). However, this study aimed to assess efficacy Propofol-Ketamine combination compared to Dexmedetomidine-Ketamine combination in sedating patients including the depth of sedation, hemodynamic, recovery time and adverse events.

METHODS

Research design

This study protocol and design was based on Meta Analysis study. Meta-analysis was conducted following the reporting recommendations of the PRISMA NMA for systematic reviews and meta-analysis (Hutton B et al., 2015).

Study Selection

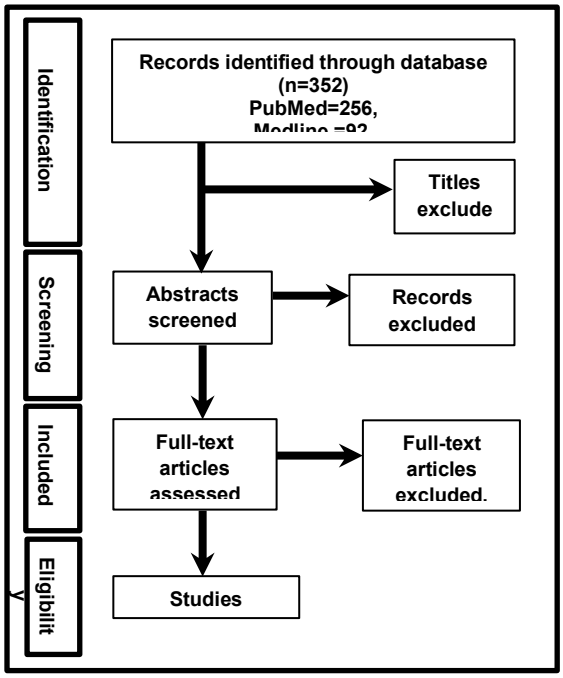

Figure 1. Flowchart of the included studies.

Studies were included in this paper if they fulfilled our PICO model which follows the inclusion criteria: Random allocation to treatment, have 2 groups randomized received Dexmedetomidine-Ketamine and Propofol-Ketamine as a combination for sedation and studies that have data about the depth of sedation, hemodynamics, recovery time or adverse events during a sedation procedure. We applied no restriction on the patient's ages. We excluded trials performed with other drug combinations, studies not reporting outcome or adverse event data, studies published as abstract only, and animal studies.

Search Strategy

The literature search was performed in several databases, such as PubMed, Medline, Cochrane and Google Scholar with the keywords Sedation Procedure, Propofol, Ketamine, Dexmedetomidine, Ketamine Combination Propofol and Ketamine Combination Dexmedetomidine from 2006 to 2022 without limitation in access or language. Total of 352 studies were identified in the initial search. After removing duplicates and nonspecific titles,

198 were screened by titles and abstracts. Obviously, irrelevant articles were excluded. The remaining 61 journals were retrieved for full-text assessment. After qualitative synthesis, we excluded 50 journals. Total 11 journals were included in this study, which consisted of 10 RCT and 1 Prospective Cohort.

Data Extraction and Quality Assessment

All included studies were reviewed in detail to assess the available data and randomization. The character information including publication data, medication, sample size and parameters was recorded. Selected parametric data were recorded in predesigned electronic files for analysis. Notably, for the extraction of adverse effects, all relative clinical effects that occurred during the trials were recorded including those in the respiratory system (such as respiratory depression or apnoe), circulatory system (such as bradycardia and hypotension), nausea and delayed recovery time.

We used Rob 2 Cochrane collaboration to assess the risk of bias (including selection, performance, detection, attrition, reporting and other bias). Any disagreements were resolved by discussion to reach a consensus.

Statistical Analysis

This study aimed to make a comprehensive comparison of Ketamine combined with Dexmedetomidine and Ketamine combined with Propofol as sedation methods. All variable and data were pooled in Excel and SPSS version 26.

Ethical Considerations

There is no ethics approval was required for this study.

RESULTS

The search yielded 61 hits journals. Total 11 studies fulfilled the inclusion criteria. These studies included a total of 754 patients who received combination therapy of sedative agents while undergoing mild to moderate medical procedures.

Sedation Procedure of Studies

All studies divided patients into 2 groups (Ketamine-Propofol group and Ketamine-Dexmedetomidine group), a dose of ketamine 1 mg/kg in both groups, Propofol 1 mg/kg and Dexmedetomidine 0.5-1μg/kg at the start of administration with a bolus or infusion. Monitoring the depth of sedation is carried out using the Sedation score and monitoring vital signs HR and MAP are carried out periodically. The administration of maintenance sedation

was not carried out in several studies and the administration of maintenance sedation in some studies was only given when the patient felt discomfort. Most of studies didn't use premedication before the sedation procedure, except five studies that used Midazolam as premedication (Tosun et al., 2006; Mogahed & Salama, 2017; Joshi et al., 2017; Singh et al., 2022).

Study Bias and Limitations

This study used RoB 2 tools, RevMan Cochrane as risk of bias tools. For assessments of bias, random sequence generation was clear in all included studies 10 RCTs and 1 Prospective Cohort, most of them described unclearly of blinding in self-reported outcomes and 2 studies have limitation in reporting the selected outcomes. Comprehensively, attrition bias revealed low risk, and half of the included studies had an unclear reporting bias.

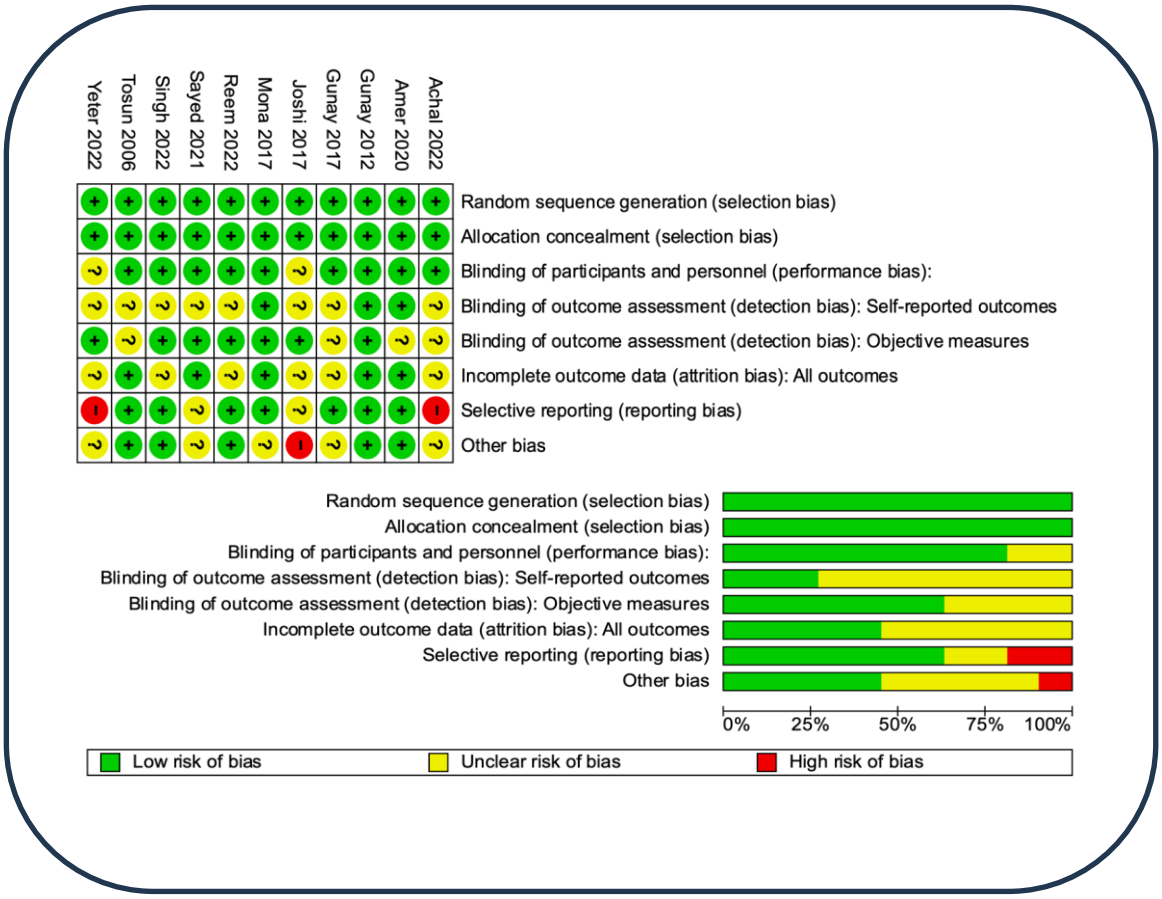

Figure 2. Methodological quality graph and summary of the

Characteristics of Patients

Total population in this study was 745 patients consisting of 404 children and 341 adults who were undergoing surgical procedures that required sedation.20-30 A total of 372 patients were in Ketamine-Dexmedetomidine group and 373 patients were in Ketamine-Propofol group with patient characteristics in this study had a mean age of 2.4 to 9.1±1.6 years and mean weight 12 to 23.6±6 kg in the pediatric population and 27 to 51±8.5 years and 75 to 84.5±4.2 kg in the adult population. ASA criteria for each patient are ASA I-IV and the most ASA criteria in patients is ASA II. The procedure time from 5.7 to 63.4 ± 5.3 minutes and also comorbidities such as Cardiology (60 patients) and Hepatic Disease (75 patients).

All studies presented monitoring data of vital signs from after induction sedation, 5 minutes, 10 minutes, 15 minutes to 30 minutes and for depth of sedation in Ramsay Scores.

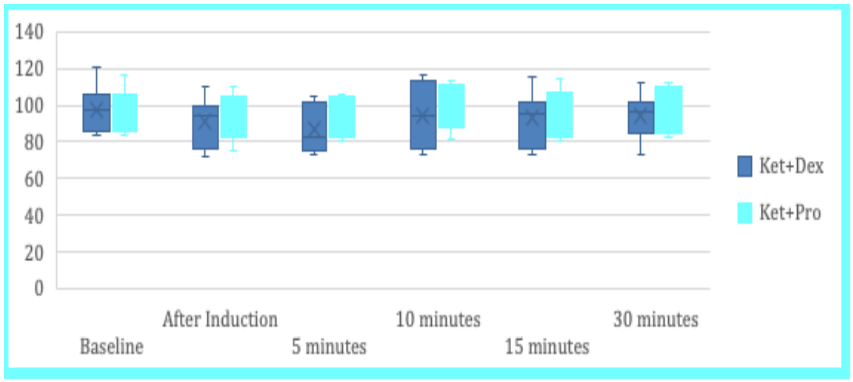

Diagram 1. Heart Rate Summary from Each Studies

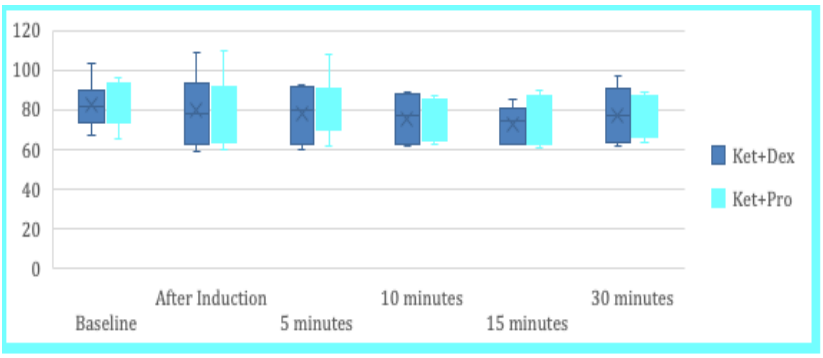

Diagram 2. MAP Summary from Each Studies

Heart Rate

Monitoring

Based on the data that has been collected, we found that there was a decrease of Heart Rate in both groups, Ketamine-Propofol group and Ketamine-Dexmedetomidine group. Heart Rate in Ketamine-Dexmedetomidine group was significantly lower compared to Ketamine-

Propofol group, especially at the time after induction up to 15 minutes after drug administration (Tosun et al., 2006; Canpolat et al., 2012; Mogahed & Salama, 2017; Joshi et al., 2017). Although there was no patient in either group that required atropine bolus (Sharkawy, 2019).

MAP Monitoring

MAP changes in both groups, Ketamine-Propofol group and Ketamine-Dexmedetomidine group were slightly decreased from their baseline value, especially after induction for up to 5 minutes after drug administration (Tosun et al., 2006). Although there was no significant difference in the two groups, the lowest MAP founded in Ketamine-Dexmedetomidine group(Singh et al., 2022).

Ramsay Sedation Score Monitoring

Most of the studies showed patients in both groups achieved Ramsay sedation score ≥3 (Raj et al., 2022). Ketamine-Dexmedetomidine group reaches faster to RSS ≥ 3 than Ketamine-Propofol group, even though Ketamine-Dexmedetomidine has longer recovery than Ketamine-Propofol group (Mogahed & Salama, 2017; Amer et al., 2020; Algharabawy et al., 2021).

Adverse Events

Hypersalivation is still reported in several studies, the Ketamine-Propofol group has a higher risk ratio rate 2.06 (0.73, 5.82 than Ketamine-Dexmedetomidine group. p=0,17. In this study we found that desaturation is the most dangerous adverse event that could happen in sedation procedure. Several studies reported desaturation in Ketamine-Propofol group was more than in Ketamine-Dexmedetomidine group risk ratio: 3.50 (1.47, 8.34) p=0,005. Odd

ratio of adverse event between the groups is 2.88 (1.48, 8.34) p=0,002.

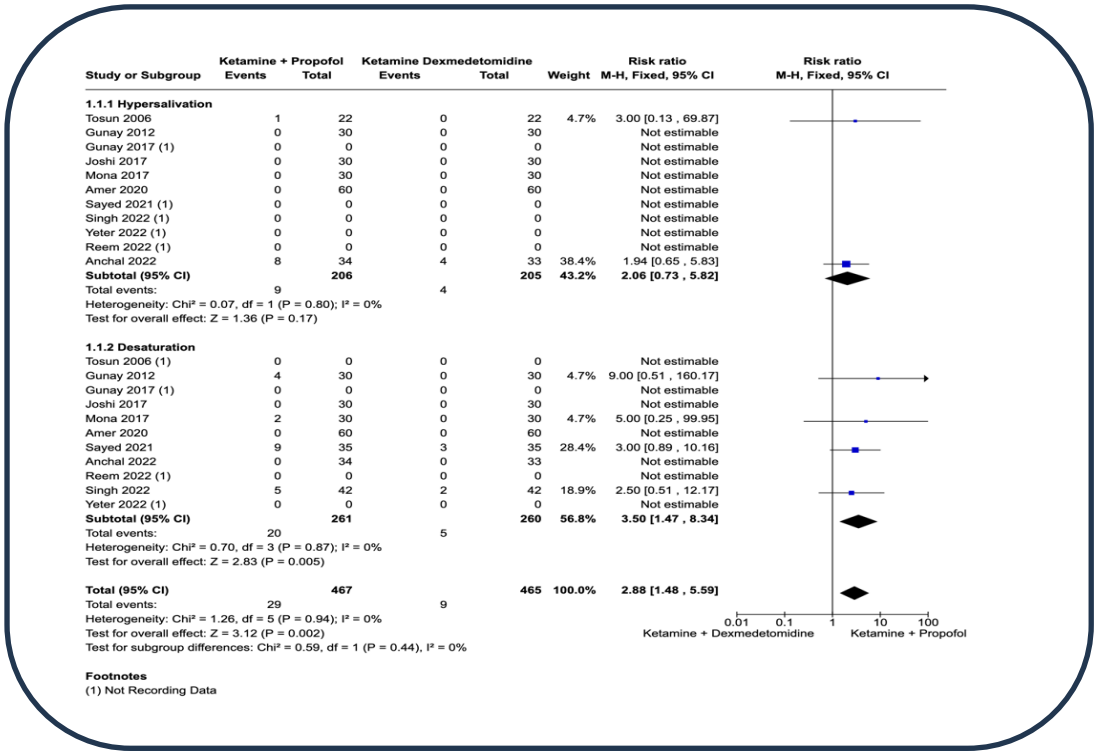

Figure 3. Adverse Events of the included studies

DISCUSSION

In sedative procedure, choosing a sedative agent should be on the basis of its onset time, associated adverse effects and time to restore cognitive function after stopping it (Curtis et al., 2013). Using propofol alone in sedation procedure, may result in respiratory and hemodynamic instability (Erden et al., 2009). The combination of Ketamine and propofol was frequently used to reduce side effects and shorten the duration of recovery in a variety of settings (Frey et al., 1999; Botero et al., 2000). Ketamine and Propofol became good anesthetic methods for several procedural sedation. Hemodynamic stability, preservation of the airway, and because Ketamine lead to dissociation alone, the Ketamine-Propofol combination preferred regimens nearly for procedural settings (Alletag et al., 2012).

Ketamine was described as safe, effective and simple and was hoped to be used as a sole anesthetic medication causing loss of consciousness, amnesia, and analgesia. Combination of Ketamine with either Propofol or Dexmedetomidine allows usage of lower doses adds synergism and decreases side effects (Ali et al., 2015). Present studies showed that the Dexmedetomidine - Ketamine combination was not superior to Propofol-Ketamine especially in pediatric patients (Berman et al., 1990; Öklü et al., 2003; Lebovic et al., 1992). Joshi et al. compared the Dexmedetomidine-Ketamine versus Propofol-Ketamine combinations on

hemodynamic stability and recovery time in 60 spontaneously breathing children undergoing cardiac catheterization. They observed decrease in the heart rate after induction in both groups, the decrease was statistically significant in the Dexmedetomidine-Ketamine group in the first 25 min after induction (Joshi et al., 2017). Yeter et al found that heart rate did not change significantly with Ketamine-Propofol and there was a slight decrease of 2 beats per minute in Ketamine-Dexmedetomidine. Both combinations showed an equally good and similar heart rate response and peripheral oxygen saturation (Yeter et al., 2022). Similar with previous research, Tosun et al found heart rate in Dexmedetomidine-Ketamine was significantly lower (average 10–20 beats/min) than Propofol-Ketamine after induction and throughout the procedure (Tosun et al., 2006).

In our study, we analyzed that there was a decrease in heart rate in both groups Ketamine-Propofol and Ketamine-Dexmedetomidine. Heart rate in Ketamine-Dexmedetomidine group was significantly lower especially at the time after induction up to 15 minutes after drug administration. One of the study described that Ketamine-Dexmedetomidine group had more haemodynamic stability (Raj et al., 2022). This result was similar to study by Gupta B et al. who compared the sedo-analgesic effects of dexmedetomidine and Ketamine-Dexmedetomidine in electively mechanically ventilated patients in surgical ICU. They found that group Dexmedetomidine experienced brief episode of hypotension and bradycardia but group Ketamine-Dexmedetomidine were hemodynamically stable.

In this regard, the study done by Mona et al. compared group Ketamine-Dexmedetomidine and group Ketamine-Propofol for sedation and analgesia in patients after coronary artery bypass surgery, found that there was insignificant difference between both the groups as regards hemodynamic stability (Mogahed & Salama, 2017). Singh et al found that intraprocedural SpO2 (SpO2 recorded every minute and averaged over procedure time) in group Ketamine-Propofol was significantly lower than group Ketamine-Dexmedetomidine (median [IQR], 97.8 96.0–98.34] vs. 98.40 [97.92–98.54] (Singh et al., 2022).

The number of episodes of significant respiratory depression was higher in group Ketamine-Propofol than in group Ketamine-Dexmedetomidine; however, the difference was not statistically significant ($p=0.589$) (Singh et al., 2022). Similarly, Amer et al. also reported an increased incidence of desaturation SpO2<92% with Ketamine-Propofol in comparison to Ketamine-Dexmedetomidine in children (Amer et al., 2020). Another study comparing the same drug combinations (Ketamine-Propofol vs. Ketamine-Dexmedetomidine) also found an increased incidence of apnea and desaturation with Ketamine-Propofol in comparison to

Ketamine-Dexmedetomidine (Mogahed & Salama, 2017). On the other hand, Gunay et.al found that Ketamine-Dexmedetomidine combination provided effective sedation with hemodynamic stability and no respiratory events (Canpolat et al., 2012).

However, Ketamine-Dexmedetomi- dine had longer induction and recovery times. In terms of side effects, the Ketamine - Dexmedetomidine combination had a lower incidence of oxygen desaturation giving the dexmedetomidine group a significant advantage in terms of respiratory safety and airway protection (Algharabawy et al., 2021). Even though, several studies reported that Ketamine-Dexmedetomidine combination has longer recovery time than Ketamine-Propofol combination (Canpolat et al., 2012; Amer et al., 2020; Yeter et al., 2022).

CONCLUSIONS

The combination of drugs in sedation procedures is the best choice to achieve a balanced effect in reducing negative side effects of drugs. Dexmedetomidine - Ketamine appears to be superior than Propofol - Ketamine in terms of hemodynamic stability, oxygen saturation and fewer adverse events even though Dexmedetomidine-Ketamine has longer recovery time and can reduce heart rate more than Propofol-Ketamine.

IMPLICATION

This study has medical implications for decision making regarding the use of drug combinations in sedation procedures and for educational materials.

STRENGTH AND LIMITATIONS

This study has strengths in monitoring vital signs and depth of sedation, but the limitation of this study is the similarity of the population which are not similar, even though the risk of bias does not show biased in this study

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CONFLICT OF INTEREST

There is no conflict of interest.

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