Effectiveness of ketamine-propofol sedation for reducing respiratory adverse events compared to propofol sedation: A Meta-Analysis of randomized controlled trials

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Abstract

Objective

The objective of our review was to determine whether ketamine-propofol had an advantage in reducing respiratory adverse events compared to propofol for procedural sedation.

Methods

Electronic databases including Web of Science, The Cochrane Library, PubMed, Medline, Embase, Google Scholar were searched to identify potential studies. All randomized controlled studies from their inception to May 2020 comparing ketamine-propofol sedation with propofol sedation were identified. Pooled analysis and subgroup analysis were conducted using Stata software. The quality assessment of all included studies was completed by using the Cochrane Collaboration’s tool for assessing risk of bias.

Results

A total of 21 studies involving 3669 individuals were included. The most common respiratory adverse events (all reported per 100 sedations) were: hypoxia(KP 10.9%; P 17.0%), respiratory depression(KP 6.9%; P 14.9%), central apnea(KP 5.9%; P 8.0%). Pooling these 21 studies, subjects with ketamine-propofol had significant lower incidence of respiratory adverse events than those with propofol (RR: 0.55, 95% CI: 0.41–0.74). When stratified by study population, no significant difference was observed in reducing respiratory adverse events between ketamine-propofol sedation and propofol sedation among children (RR: 0.74, 95% CI: 0.46–1.20). However, significant differences were discerned definitely among adults(RR: 0.48, 95% CI: 0.39–0.60).

Conclusion

In summary, Our results suggested hypoxia, respiratory depression, central apnea were most common respiratory adverse events in propofol sedation. However, ketamine-propofol sedation had an advantage in reducing the incidence of respiratory adverse events compared with propofol sedation, especially in adults.

Introduction

Procedural sedation is the use of sedative and dissociative drugs to provide sedation and motor control during painful or unpleasant diagnostic and therapeutic procedures. In the last few decades, this procedure has become an important part of clinical practice for each physician. A reliable sedation method must be both effective and safe. It is hard to meet this requirement for a single drug. So combining different sedative and dissociative drugs for procedural sedation has attracted the attention of researchers.

As a solitary agent, propofol is widely used for procedural sedation. Although propofol is able to achieve rapid and effective sedation, it may cause some respiratory adverse events. Recently some researchers have found the use of a ketamine-propofol combination for procedural sedation has an advantage in reducing respiratory adverse events compared to propofol sedation[17, 18, 19].

Here, we searched all randomized controlled trials reporting ketamine-propofol sedation versus propofol sedation for procedural sedation. Pooled analysis and subgroup analysis were conducted to determine whether ketamine-propofol had an advantage in reducing respiratory adverse events compared to propofol sedation. Understanding the effectiveness of ketamine-propofol sedation for reducing respiratory adverse events compared to propofol sedation would help in determining preferred medications used for procedural sedation.

Materials And Methods

Data sources

Electronic databases including Web of Science, The Cochrane Library, PubMed, Medline, Embase, Google Scholar were searched to identify potential studies. All randomized controlled trials from their inception to May 2020 reporting ketamine-propofol sedation versus propofol sedation for reducing respiratory adverse events were included. There were no language restrictions. The above search strategy was implemented with the following keywords: “ketofol” OR “ketamine” OR “ketanest” OR “ketalar” AND ”propofol” AND “adverse events” OR “complications”.

Inclusion and Exclusion Criteria
Included studies met the following criteria: (i) randomized controlled trials, (ii) human studies comparing effectiveness of ketamine-propofol sedation with propofol sedation for reducing respiratory adverse events (see Table 1), (iii) the incidence of respiratory adverse events could be compared between patients with ketamine-propofol and propofol. We excluded ineligible studies according to the following criteria: (i) Studies reporting the other sedative agents for procedural sedation were excluded, (ii) overlapping with previous published data or articles.

Quality assessment

The quality assessment of all included studies was completed by using the Cochrane Collaboration's tool for assessing risk of bias (see Figure 1). Risk of bias tables for every study included the following domains: random sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcomes assessment, incomplete outcome data, and selective outcome reporting. If there were different opinions, we discussed to decide the final conclusion. Two researchers respectively performed the risk of bias assessment.

Data Extraction

According to search strategy, two researchers respectively screened potential literature, and identified eligible studies. After reading full text of included studies, they created a database to extract baseline data of each study, including name of authors, publication year, study design, number of individuals, were extracted the data on name of the first author, number of patients in the analysis, outcome variables.

Statistical Analysis

All data about the incidence of respiratory adverse events were binary count data, reported as risk ratio (RR). RR was calculated by dividing the "risk of respiratory adverse events in ketamine-propofol group" by the "risk of respiratory adverse events in propofol group". The Cochran's Q test (significance level at \( P < 0.10 \)) was used to estimate heterogeneity among included studies. The \( I^2 \) statistic was also used to quantify heterogeneity across studies. If \( I^2 \) was more than 50%, which prompted that there was potential heterogeneity, random effects model was chose to pool data. On the contrary, fixed effects model was chose. Egger's test was used to assess the publication bias. According to the distribution of respiratory adverse events, subgroup analysis were conducted to explore the potential sources of heterogeneity.

Results

Characteristics of Studies

After searching electronic databases including Web of Science, The Cochrane Library, PubMed, Medline, Embase, Google Scholar, 1412 potentially titles were reviewed. According to search strategy, 1332 studies were excluded. Only 81 studies were preliminarily identified and went forward to the data extraction stage. After reviewing the full-texts of those studies, 14 studies were excluded for irrelevant studies, 26 were excluded for studies assessing other medications, 13 were excluded for animal studies, 7 observational studies were also excluded. Therefore, 21 studies were included into the meta-analysis to pool data (Figure 2). The main characteristics of those 21 studies were listed in the Table 2.

Table 3 showed the distribution of respiratory adverse events. The most common respiratory adverse events (all reported per 100 sedations) were: hypoxia (KP 10.9%; P 17.0%), respiratory depression (KP 6.9%; P 14.9%), central apnea (KP 5.9%; P 8.0%).

Respiratory adverse events

After pooling these 21 studies, subjects with ketamine-propofol had significant lower incidence of respiratory adverse events than those with propofol (RR: 0.55, 95% CI: 0.41–0.74) (see Figure 3). \( I^2 \) was 60.0%, which prompted that there was potential heterogeneity.

When stratified by study population, no significant difference was observed in reducing respiratory adverse events between ketamine-propofol sedation and propofol sedation among children (RR: 0.74, 95% CI: 0.46–1.20). However, significant differences were discerned definitely among adults (RR: 0.48, 95% CI: 0.39–0.60). (See Table 4).

Test of Heterogeneity and Publication Bias

Pooling all included studies, \( I^2 \) was 60.0%, which prompted that there was mild heterogeneity. But after implementing the stratified analysis, \( I^2 \) was 46.6% in children, 50.7% in adults, which indicated the population factor may be the source of heterogeneity. Egger's test was used to assess the publication bias. P value was greater than 0.05, which revealed the absence of publication bias.

Discussion
As a normative method of managing sedation and analgesia agents, procedural sedation and analgesia (PSA) was administered by physicians in almost all clinical departments[22]. Since first proposed decades before, PSA was implemented by using many agents such as morphine, ketamine, propofol. But each of them has advantages and disadvantages. In order to alleviate patients' unpleasant procedures, medications must be both effective and safe.

There were two pharmacologic approaches applied in administering PSA[23]. The first pharmacologic approach was single agent approach, which always applied to specific clinical situation, and may cause some adverse events. The other pharmacologic approach was a balanced agent approach, which allowed a combination of 2 or more agents, and may produce a complementary effect.

Recently some researchers paid attention to the use of a ketamine-propofol combination for PSA[17, 18, 19]. A portion of them supported that ketamine-propofol had an advantage in reducing respiratory adverse events compared to propofol sedation. But some of them obtained negative results. So we implemented the meta-analysis to determine whether ketamine-propofol had an advantage in reducing respiratory adverse events compared to propofol sedation.

According to the distribution of respiratory adverse events, the most common respiratory adverse events in propofol sedation were: hypoxia, respiratory depression, central apnea. The cause of the results may be due to propofol reduces genioglossus muscle activity. The low activity of genioglossus muscle increases airway resistance, and increases the collapsibility of the upper airway. This can aggravate obstructive sleep apnea in patients sedated with propofol. Obstructive sleep apnea leads to increased transmural left and right ventricular pressures, increased sympathetic activity like increased blood pressure and heart rate, and alveolar hypoxia and hypercapnia which may cause pulmonary arteriolar vasoconstriction leading to increased pulmonary artery pressures. So it is also known as a risk factor for heart failure and pulmonary hypertension. The use of a ketamine-propofol combination for procedural sedation may have an advantage in reducing the incidence of such complications.

When stratified by study population, no significant difference was observed in reducing respiratory adverse events between ketamine-propofol sedation and propofol sedation among children (RR: 0.74, 95% CI: 0.46–1.20). However, significant differences were discerned definitely among adults (RR: 0.48, 95% CI: 0.39–0.60). The cause of the results may be due to there were a lower plasma clearance of propofol in children than that of in adults. Some studies had found the variability in plasma clearance and subsequent influence on plasma concentrations may potentially impact on the incidence of propofol(ketamine) adverse effects[24, 25].

**Limitations**

Similar to other systematic reviews and meta-analyses, our results are limited by clinical trial quality. And there are substantial statistical and clinical heterogeneity. Different studies have different dose standards for anesthetics. Some of the trials used an initial dose of approximately 1 mg/kg of the study drug in the propofol group, but comparators varied with respect to the initial dose, ratios, and administration of the study drug in the K-P group.

**Conclusion**

Our results suggested hypoxia, respiratory depression, central apnea were most common respiratory adverse events in propofol sedation. However, ketamine-propofol sedation had an advantage in reducing the incidence of respiratory adverse events compared with propofol sedation, especially in adults.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and material**

All data generated or analysed during this study are included in this published article. Please contact the author for further data requests.

**Competing interests**
The authors declare that they have no competing interests.

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**Authors’ contributions**

TW and SBC designed the study. LLZ and YZ made an analysis of data and drafted the manuscript. All authors took part for a writing process, and approved the final manuscript.

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Tables

Table 1  Definition of the respiratory adverse events

| Item                                | Definition                                                                                                                                 |
|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Hypoxia                             | An oxygen saturation of <92% at any time during the procedure                                                                            |
| Central apnea                       | A pause in respiratory effort, defined as an absent end tidal CO₂ waveform>6 s during the procedure                                      |
| Respiratory depression              | Hypopneic hypoventilation, defined as a decrease in ETCO₂>10 mmHg recorded during the procedure or by physician report of partial upper airway obstruction |
| Complete upper airway obstruction   | Ventilatory effort without air exchange, defined by an absent ETCO₂ waveform with physician report of ventilatory effort              |
| Laryngospasm                        | Partial or complete airway obstruction caused by involuntary closure of the vocal cords not relieved by routine airway repositioning or insertion of a nasal or oral airway, by physician report |

Table 2  The quality assessment of all included trials in our study
| Study               | Random sequence generation | Allocation concealment | Blinding of participants/personnel | Blinding of outcomes assessment | Incomplete outcome data | Selective outcome reporting |
|---------------------|-----------------------------|------------------------|------------------------------------|---------------------------------|-------------------------|-----------------------------|
| David 2011[1]       | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Andolfatto 2012[2]  | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Sawas 2013[3]       | Low                         | Unclear                | Unclear                            | High                            | Low                     | Low                         |
| Miner 2015[4]       | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Ferguson 2016[5]    | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Frizelle 1997[6]    | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Frey 1999[7]        | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Badrinath 2000[8]   | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Vora 2005[9]        | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Singh 2010[10]      | Low                         | Unclear                | Unclear                            | High                            | Low                     | Low                         |
| Chiaretti 2011[11]  | Low                         | Unclear                | Unclear                            | High                            | Low                     | Low                         |
| Abdellatif 2012[12] | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Fabbri 2012[13]     | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Aydogan 2013[14]    | Low                         | Unclear                | Unclear                            | High                            | Low                     | Low                         |
| Yuce 2013[15]       | Low                         | Unclear                | Unclear                            | High                            | Low                     | Low                         |
| De Oliveira 2014[16]| Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Tandon 2014[17]     | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Canpolat 2016[18]   | Low                         | Unclear                | Unclear                            | High                            | Low                     | Low                         |
| Tutil 2016[19]      | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Kapadia 2018[20]    | Low                         | Unclear                | Unclear                            | High                            | Low                     | Low                         |
| Schmitz 2018[21]    | Low                         | Low                    | Low                                | High                            | Low                     | Low                         |
| Summary score       | Low risk of bias            | Unclear risk of bias   | Unclear risk of bias               | High risk of bias               | Low risk of bias         | Low risk of bias            |

Table 3  The main characteristics of 21 included studies in our meta-analysis
| Study            | Dose of K-P | Dose of propofol | Route of treatment | Number of Participants | Procedure                                                                 |
|------------------|-------------|------------------|--------------------|------------------------|---------------------------------------------------------------------------|
| David 2011       | 0.5 mg/kg K, 1 mg/kg P | 1 mg/kg          | intravenous         | 193                    | fracture/dislocation, Suturing, Foreign body removal, Chest tube insertion |
| Andolfatto 2012  | 0.75 mg/kg K-P | 0.75 mg/kg       | intravenous         | 284                    | fracture/dislocation, Incision and drainage, Laceration repair, Chest tube insertion, Cardioversion |
| Sawas 2013       | Unclear     | Unclear          | intravenous         | 99                     | emergency Incision, drainage of abscess and cardioversion                |
| Miner 2015       | 0.5 mg/kg K-P | 1 mg/kg          | intravenous         | 271                    | emergency Incision, drainage of abscess and cardioversion                |
| Ferguson 2016    | 0.5 mg/kg K-P | 0.5 mg/kg        | intravenous         | 573                    | fracture reduction, drainage of abscess, Shoulder reduction and cardioversion |
| Frizelle 1997    | 0.1 mg/kg K, 0.4 mg/kg P | 0.5 mg/kg      | intravenous         | 34                     | orthopedic                                                               |
| Frey 1999        | 30 mg K, 100 mg P | 100 mg          | intravenous         | 39                     | retrobulbar block                                                        |
| Badrinath 2000   | 0.94-1.88mg/ml K, 9.4mg/ml P | 9.4mg/ml      | intravenous         | 58                     | breast biopsy                                                             |
| Vora 2005        | 10ml 1 % P, 10ml 0.5 % K | 20ml1 % P      | intravenous         | 53                     | gynaecological                                                            |
| Singh 2010       | 0.4 mg/kg K, 1.6 mg/kg P | 2 mg/kg         | intravenous         | 36                     | abdominal surgeries                                                       |
| Chiaretti 2011   | 0.5 mg/kg K, 2 mg/kg P | 2 mg/kg         | intravenous         | 113                    | lumbar punctures, bone marrow aspirations                                 |
| Abdellatif 2012  | 0.83 mg/kg K, 0.83 mg/kg P | 0.83 mg/kg     | intravenous         | 75                     | digital rectal examination                                                |
| Fabbri 2012      | 5 μg/kg/min K, 1 mg/kg/h P | 1 mg/kg/h       | intravenous         | 288                    | endoscopic retrograde cholangiopancreatograhy                             |
| Aydogan 2013     | 5mg K, 15mg P | 20mg             | intravenous         | 99                     | gastrointestinal endoscopy                                                |
| Yuce 2013        | Unclear     | Unclear          | intravenous         | 150                    | dilatation and curettage                                                  |
| De Oliveira 2014 | 0.5mg/kg K, 6.5 mg/kg P | 6mg/kg          | intravenous         | 47                     | breast lumpectomony                                                      |
| Tandon 2014      | 0.15 mg/kg K, 152 mg P | 167 mg          | intravenous         | 247                    | upper gastrointestinal endoscopy                                         |
| Canpolat 2016    | 0.5 mg/kg K, 0.5 mg/kg P | 1 mg/kg         | intravenous         | 37                     | tooth extraction                                                          |
| Tutil 2016       | 0.5 mg/kg K-P | 0.5mg/kg         | intravenous         | 86                     | colonoscopy                                                              |
| Kapadia 2018     | Unclear     | Unclear          | intravenous         | 28                     | magnetic resonance imaging                                               |
| Schmitz 2018     | 1mg/kg K, 5 mg/kg/h P | 10 mg/kg/h     | intravenous         | 287                    | magnetic resonance imaging                                               |
Table 4  The distribution of respiratory adverse events in 21 included studies
| Study              | Respiratory adverse events |     |     | Respiratory depression |     |     | Complete upper airway obstruction |     |     |
|-------------------|----------------------------|-----|-----|------------------------|-----|-----|-----------------------------------|-----|-----|
|                   |                            | KP(%)| P(%)| KP(%)                  | P(%)| KP(%)| P(%)                              | KP(%)| P(%)|
| David 2011        |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Andolfatto 2012   |                            | 38/142 (26.8) | 36/142 (25.4) | 15/142 (10.6) | 13/142 (9.2) | NA | NA | 6/142 (4.2) | 4/142 (2.8) | 0/142 (0.0) | 0/142 (0.0) |
| Sawas 2013        |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Miner 2015        |                            | 6/85 (7.1) | 11/90 (12.2) | 6/85 (7.1) | 11/90 (12.2) | 16/85 (18.8) | 15/90 (16.7) | NA | NA | 0/85 (0.0) | 0/90 (0.0) |
| Ferguson 2016     |                            | 17/281 (6.0) | 23/292 (7.9) | 11/281 (3.9) | 16/292 (5.5) | 3/281 (1.1) | 13/292 (4.5) | NA | NA | NA | NA |
| Frizelle 1997     |                            | 2/20 (10.0) | 3/20 (15.0) | 0/20 (0.0) | 1/20 (5.0) | NA | NA | NA | NA | NA | NA |
| Frey 1999         |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Badrinath 2000    |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Vora 2005         |                            | NA   | NA   | 4/30 (13.3) | 12/30 (40.0) | NA | NA | NA | NA | NA | NA |
| Singh 2010        |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Chiaretti 2011    |                            | 1/59 (1.7) | 7/62 (11.3) | NA | NA | NA | NA | NA | NA | NA | NA |
| Abdellatif 2012   |                            | 4/35 (11.4) | 29/35 (82.9) | NA | NA | NA | NA | NA | NA | NA | NA |
| Fabbri 2012       |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Aydogan 2013      |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Yuce 2013         |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| De Oliveira 2014  |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Tandon 2014       |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
| Canpolat          |                            | NA   | NA   | NA                     | NA  | NA   | NA                                | NA   | NA  |
Table 5 Subgroup analysis

| Item   | Number of studies | Pooled OR (95% CI) | Heterogeneity (%) |
|--------|-------------------|--------------------|-------------------|
| In children | 5                  | 0.74 (0.46-1.20)   | 46.6              |
| In adults  | 13                 | 0.48 (0.39-0.60)   | 50.7              |

Figures

Figure 1
Flow chart of study selection process
| Study ID       | RR (95% CI)          | Weight |
|---------------|----------------------|--------|
| David 2011    | 0.81 (0.49, 1.35)    | 8.58   |
| Andolfatto 2012| 0.95 (0.66, 1.37)    | 9.79   |
| Sawas 2013    | 0.81 (0.55, 1.22)    | 9.48   |
| Miner 2015    | 0.90 (0.61, 1.34)    | 9.51   |
| Ferguson 2016 | 0.82 (0.47, 1.42)    | 8.27   |
| Frizelle 1997 | 0.50 (0.10, 2.43)    | 2.73   |
| Frey 1999     | 0.50 (0.26, 0.95)    | 7.53   |
| Badrinath 2000| 0.74 (0.46, 1.19)    | 8.90   |
| Vora 2005     | 0.07 (0.00, 1.12)    | 1.03   |
| Singh 2010    | 0.33 (0.04, 2.94)    | 1.63   |
| Chiaretti 2011| 0.15 (0.02, 1.18)    | 1.78   |
| Abdellatif 2012| 0.08 (0.03, 0.20)   | 5.19   |
| Fabbri 2012   | 0.36 (0.17, 0.75)    | 6.81   |
| Aydogan 2013  | 0.33 (0.01, 7.99)    | 0.83   |
| Yuce 2013     | 1.00 (0.06, 15.70)   | 1.07   |
| De Oliveira 2014| 0.14 (0.01, 2.63)   | 0.97   |
| Tandon 2014   | 0.21 (0.07, 0.60)    | 4.75   |
| Canpolat 2016 | 0.14 (0.01, 2.60)    | 0.88   |
| Tural 2016    | 0.05 (0.00, 0.86)    | 1.03   |
| Kapadia 2018  | 0.20 (0.01, 3.85)    | 0.94   |
| Schmitz 2018  | 1.18 (0.68, 2.05)    | 8.23   |
| Overall (I-squared = 80.0%, p = 0.000) | 0.55 (0.41, 0.74) | 100.00 |

**Figure 2**

Forest plot of studies comparing ketamine-propofol with propofol in respiratory adverse events.