Ketamine-Propofol Combination (Ketofol) Versus Propofol Alone for Emergency Department Procedural Sedation and Analgesia: A Randomized Double-Blind Trial

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Study objective: We determine whether a 1:1 mixture of ketamine and propofol (ketofol) for emergency department (ED) procedural sedation results in a 13% or more absolute reduction in adverse respiratory events compared with propofol alone.

Methods: Participants were randomized to receive either ketofol or propofol in a double-blind fashion. Inclusion criteria were aged 14 years or older and American Society of Anesthesiology class 1 to 3 status. The primary outcome was the number and proportion of patients experiencing an adverse respiratory event as defined by the Quebec Criteria. Secondary outcomes were sedation consistency, efficacy, and time; induction time; and adverse events.

Results: A total of 284 patients were enrolled, 142 per group. Forty-three (30%) patients experienced an adverse respiratory event in the ketofol group compared with 46 (32%) in the propofol group (difference 2%; 95% confidence interval [CI] 9% to 13%; \(P = .80\)). Three ketofol patients and 1 propofol patient received bag-valve-mask ventilation. Sixty-five (46%) patients receiving ketofol and 93 (65%) patients receiving propofol required repeated medication dosing or progressed to a Ramsay Sedation Score of 4 or less during their procedure (difference 19%; 95% CI 8% to 31%; \(P = .001\)). Six patients receiving ketofol were treated for recovery agitation. Other secondary outcomes were similar between the groups. Patients and staff were highly satisfied with both agents.

Conclusion: Ketofol for ED procedural sedation does not result in a reduced incidence of adverse respiratory events compared with propofol alone. Induction time, efficacy, and sedation time were similar; however, sedation depth appeared to be more consistent with ketofol. [Ann Emerg Med. 2012;59:504-512.]

Please see page 505 for the Editor’s Capsule Summary of this article.

INTRODUCTION

Procedural sedation and analgesia is used in the emergency department (ED) to efficiently and humanely perform necessary painful procedures.\(^1\) Ketamine and propofol are 2 medications commonly used for this purpose because they possess many characteristics deemed desirable by clinicians.\(^2,3\) However, ketamine use is limited by its propensity to cause emesis and recovery agitation, and by its prolonged recovery time compared with that of propofol.\(^4,5\) Propofol itself is limited by dose-dependent hypotension and respiratory depression,\(^6,8\) especially when combined with opioids.\(^3,13\) The opposing physiologic effects of ketamine and propofol suggest the potential for synergy, and this has led to interest in their combined use, commonly termed “ketofol,” to facilitate ED procedural sedation.\(^14-16\) The use of ketofol has been described in numerous non-ED settings,\(^17,21\) and its use for ED procedural sedation has been accomplished with each drug in separate syringes, as well as mixed in the same syringe.\(^22-29\) The combination has been demonstrated to be chemically stable and physically compatible when mixed in polypropylene syringes.\(^28,29\)

The potential advantages of ketofol over propofol alone include the provision of deep sedation with lower doses of...
propofol, thus potentially limiting propofol-associated adverse respiratory effects; the provision of ketamine analgesia without the increased adverse respiratory effects associated with concomitant opioid administration; and the mitigation of propofol-induced hypotension. The potential advantages of ketofol over ketamine-alone procedural sedation include shorter recovery time and a lower incidence of ketamine-associated emesis and recovery agitation.26,32

Importance
The potential synergy of ketamine and propofol used in combination may result in fewer adverse respiratory events than when propofol is used alone for ED procedural sedation.

Goals of This Investigation
Our goal was to determine whether a single-syringe mixture of ketamine and propofol in a 1:1 ratio for ED procedural sedation in patients aged 14 years or older results in a 13% or more absolute reduction in adverse respiratory events as described by predefined criteria (the Quebec Criteria) when compared with propofol alone.

MATERIALS AND METHODS

Study Design
This was a randomized, double-blind trial approved by the University of British Columbia Clinical Research Ethics Board. Before study launch, the methods were registered with ClinicalTrials.gov (NCT01211158), and a “no objection letter” was obtained from Health Canada (file no. 9427-2649-21C).

Subjects were assigned to receive either propofol or ketofol by a computer-generated block randomization schedule, with variable block sizes to a maximum of 10.

Setting and Selection of Participants
The study was performed between December 2010 and September 2011 at Lions Gate Hospital, a 250-bed community teaching hospital and Level III trauma center with an annual ED census of 51,000 visits, of which 80% are by adults. The ED is staffed by 21 full-time emergency physicians certified by the Canadian College of Family Physicians or the Royal College of Physicians and Surgeons of Canada. All emergency physicians on staff were trained in, and participated in, subject recruitment and conduct of the study protocol. Of 100 registered nurses on staff, 50 were trained in the preparation of the study medications. The ED respiratory therapy staff consisted of 17 members, 14 of whom were trained in the study protocol.

Eligible patients were identified by the treating emergency physician. Inclusion criteria were requirement for procedural sedation as determined by the treating emergency physician, aged 14 years or older, and American Society of Anesthesiology class 1 to 3 status. Patients were excluded if they were unable to give informed consent, were pregnant, or had a known allergy to either study medication.

Procedure consent was obtained by the treating emergency physician in accordance with regional ED procedural sedation guidelines. Study consent was obtained by the respiratory therapist or the treating emergency physician before randomization.

Interventions
The randomization schedule and study medications were overseen by the ED pharmacist and stored in the ED in a medication dispensing system (Omnicell, Inc, Mountain View, CA) that electronically recorded all medication dispensed. The pharmacist was not involved in patient recruitment or in procedural sedation activities. Study medications were stored in unopened vials, along with a blank, sealed unblinding envelope, inside which was a label identifying the study drug. This envelope was available to be opened during the procedure only if clinically necessary at the discretion of the treating emergency physician.

After informed consent was obtained, a trained registered nurse (the “study nurse”), not involved in either subject recruitment or the sedation procedure, was asked by the respiratory therapist or by the treating emergency physician to prepare study medication. After accessing the randomization schedule and preparing the directed study medication, the study nurse placed the study sequence number sticker on the study drug syringe.

All study medications were prepared in identical 20-mL polypropylene syringes. Propofol-alone syringes contained propofol 10 mg/mL. Ketofol syringes were prepared as a 1:1
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mixture of 10 mg/mL ketamine and 10 mg/mL propofol; thus, each mL of medication in the ketofol syringes contained 5 mg each of ketamine and propofol. All syringes were identical and were labeled only with a sequence number. The study medications were prepared and delivered to the procedure room, along with the blank sealed unblinding envelope, by the study nurse.

Subjects received preprocedural analgesia at the discretion of the treating emergency physician. A minimum 30-minute washout period between the administration of any opioid analgesic and the commencement of the sedation procedure was mandated. All procedures were carried out in the ED in an area equipped with an airway and resuscitation cart. All patients received continuous pulse oximetry, capnography, and cardiac monitoring. No preoxygenation was provided.

Sedations were attended by a respiratory therapist, a registered nurse, and 2 emergency physicians. One emergency physician was responsible for conducting the procedure (the treating physician), whereas the other emergency physician (the sedation physician) was responsible for administering the study medication according to a preprinted weight-based protocol. Subjects received an initial dose of 0.075 mL/kg of study medication (either 0.75 mg/kg of propofol or 0.375 mg/kg each of ketamine and propofol), administered during 15 to 30 seconds. One minute after the initial dose and every minute thereafter, the sedation physician assessed the patient’s level of sedation with the Ramsay Sedation Scale (Table E1, available online at http://www.annemergmed.com). If the sedation physician determined that the Ramsay Sedation Score was less than 5, additional study medication was administered at a dose of 0.375 mL/kg (either 0.375 mg/kg of propofol or 0.188 mg/kg each of ketamine and propofol) during 15 to 30 seconds. The procedure commenced when the patient achieved deep sedation (Ramsay Sedation Score 5 or greater). All patients wore reflective sunglasses to obscure any nystagmus, or lack thereof, that could potentially identify the study drug.

Data Collection and Processing

Data collection was performed on data sheets separate from the clinical record. Before the sedation, the respiratory therapist recorded patient demographic data, study sequence number, American Society of Anesthesiology class, time of last analgesic administration, and pain severity on a scale from 1 to 10.

During the procedure, the respiratory therapist recorded the number of milliliters of study drug administered and the patient’s Ramsay Sedation Score, as determined by the sedation physician, every minute, as well as the time of first medication dose given (sedation start time). Procedure start and completion times were determined by the treating physician and recorded by the respiratory therapist. Blood pressure was performed every 4 minutes with an automated cuff and recorded by the respiratory therapist. Continuous capnography, pulse oximetry, respiratory rate, and pulse rate were recorded electronically with an Oridion Capnostream-20 capnography monitor (Oridion Capnography Inc, Needham, MA).

During the procedure and recovery period, the respiratory therapist determined and recorded whether any adverse respiratory events occurred according to explicit criteria (see “Outcome Measures”). All adverse events were recorded on the study sheets by means of specific event checkboxes, as well as a free-text area in which any additional events could also be noted.

Patient recovery was assessed by the registered nurse every 2 minutes, according to a Modified Aldrete Scale (Table E2, available online at http://www.annemergmed.com). The time of recovery was recorded on the study sheet by the respiratory therapist. After recovery, the respiratory therapist queried subjects about the quality of their sleep and whether they had any recall of the procedure, according to a 10-point scale (anchored with 1 = “not at all effective”; 10 = “extremely effective”). The treating physician recorded any incidence of agitation or rigidity during the procedure significant enough to interfere with conduct of the procedure. The registered nurse recorded any instances of recovery agitation (restlessness, confusion, dysphoria, or unpleasant dreams) occurring during the recovery phase.

The registered nurse and the sedation physician recorded their satisfaction with the sedation by using a 10-point scale (anchored with 1 = “not satisfied”; 10 = “extremely satisfied”). After completion of the procedure, the respiratory therapist, the registered nurse, and both emergency physicians recorded which of the study medications they believed was used by circling either “ketofol” or “propofol” on the study sheet, and the sealed envelope containing the identity of the medication was destroyed unopened.

Data were entered in Microsoft Excel (Version 14.1.4, Microsoft, Redmond, WA) for tabulation and analysis by a single research assistant, who was uninvolved in subject recruitment or the sedation procedures.

Outcome Measures

The primary outcome was the number and proportion of patients experiencing a respiratory adverse event as defined by the Quebec Criteria, and is described in detail in Table 1. These definitions are taken from the consensus-based recommendations for standardizing procedural sedation and analgesia terminology and reporting of adverse events put forth by Bhatt et al and use an intervention-based framework designed to result in more standardized and accurate data collection for clinically important events.

Secondary outcomes included sedation consistency, total medication dosage, sedation efficacy, induction time, procedure time, sedation time, recovery time, and the incidence of adverse events. Sedation consistency was defined as the number and proportion of patients maintaining a Ramsay Sedation Score of 5 or greater throughout the entire procedure or not requiring additional medication administration for completion of the procedure. Sedation was considered efficacious if the patient did not have unpleasant recall of the procedure, experience a sedation-related adverse event resulting in abandonment of the
procedure, or have any adverse event resulting in unplanned prolonged ED observation (3 or more hours, as defined by regional ED sedation guideline) or unplanned admission to the hospital, as determined by the treating physician. Induction time was defined as the interval from first dose of medication administered until the time that a Ramsay Sedation Score of 5 was reached or the procedure was begun. The number of doses of medication required to achieve a Ramsay Sedation Score of 5 was also compared. Sedation time was defined as time from first medication administration to time of procedure completion. Procedure start and end times were determined by the treating physician and recorded by the respiratory therapist. Recovery time was defined as the interval from the last dose of medication administered until discharge criteria were met.

Adverse events recorded were vomiting, rash, bradycardia (decrease in pulse rate requiring administration of medications or chest compressions), hypotension (systolic blood pressure decrease requiring administration of fluid bolus or vasopressors), procedural agitation (patient combativeness interfering with procedure, including paradoxic response to medication and reactivity to painful manipulation), and recovery agitation (restlessness, confusion, dysphoria, and unpleasant dreams). Treatment for recovery agitation was defined as either physical restraint or the use of sedative medication. Other adverse events recorded were muscular rigidity interfering with the procedure, use of reversal agents for opioids or benzodiazepines, and unexpected hospital admission because of sedation-related factors, as determined by the treating physician.

**Primary Data Analysis**

Group sizes were determined after evaluation of the published evidence on both propofol and ketofol, and analysis of case series data collected at the study institution with regard to the rate of adverse respiratory events, as defined by the Quebec Criteria. A respiratory adverse event rate of 21% (95% confidence interval [CI] 19.1% to 23.0%) was anticipated after review of previous studies on propofol according to prespecified criteria (propofol alone administered by intermittent bolus, 30-minute “washout” period after opioid use, patients aged 14 years or older, and study performed in an ED less than 10 years previously). There was no attempt to stratify studies by dosing regimen. For ketofol, a respiratory adverse event rate of 8% (95% CI 5.9% to 10.7%) was anticipated after review of the available literature and data from a case series at the study facility. Using the 13% absolute difference in adverse respiratory events found when comparing these data, we calculated that 129 subjects in each group would be required to have 80% power to detect a difference of this magnitude or greater (α .05, 2-sided calculation). An additional 10% was added to the enrollment to offset potential dropouts, resulting in a total sample size of 284 subjects (142 in each group).

Analysis was by intention to treat. It was decided a priori to formally compare point and interval estimates with Fisher’s exact test for the primary outcome and the sedation consistency measure. No adjustments for multiple comparisons were performed. Data on the number and proportion of patients experiencing a respiratory adverse event were stratified by treatment group. Ninety-five percent CIs for the differences between the groups were determined with Newcombe’s Method 10.36 All other secondary outcomes were reported with descriptive statistics (Microsoft Excel, Version 14.1.4). Categorical data are presented as frequency and percentage of frequency of occurrence. Continuous data are presented as medians and quartile ranges. Ninety-five percent CIs are reported for frequencies of adverse events.

**RESULTS**

**Characteristics of Study Subjects**

The flow of study subjects is illustrated in Figure 1, which represents all patients sedated during the study period. There were no cases of sedations occurring with agents other than ketofol or propofol. The 2 groups were similar with regard to demographic characteristics and procedures performed (Table 2). The most commonly performed procedures were orthopedic, comprising 60% of each group. Fifty-nine

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**Table 1. Quebec Criteria adverse respiratory events.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen desaturation</td>
<td>A decrease in oxygen saturation resulting in any of the following: vigorous tactile stimulation, airway repositioning, suctioning, supplemental oxygen delivery, any airway placement, bag-valve-mask ventilation</td>
</tr>
<tr>
<td>Central apnea</td>
<td>Cessation of ventilatory effort* resulting in any of the following: vigorous tactile stimulation, airway repositioning, bag-valve-mask ventilation, any airway placement</td>
</tr>
<tr>
<td>Partial upper airway obstruction</td>
<td>The occurrence of stridor or snoring responding to airway repositioning, airway placement, or suctioning</td>
</tr>
<tr>
<td>Complete upper airway obstruction</td>
<td>Ventilatory effort with no air exchange† resulting in any of the following: airway repositioning, suctioning, bag-valve-mask ventilation, any airway placement</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>Partial or complete upper airway obstruction, with oxygen desaturation caused by involuntary and sustained closure of the vocal cord not relieved by airway repositioning, suctioning, or oral/nasal airway insertion</td>
</tr>
<tr>
<td>Clinically apparent pulmonary aspiration</td>
<td>The presence before the end of the recovery phase of new physical symptoms (cough, crackles/rales, decreased breath sounds, tachypnea, wheeze, rhonchi, respiratory distress), or requirement for supplemental oxygen to maintain baseline oxygenation, or chest radiograph findings of focal infiltrate, consolidation, or atelectasis</td>
</tr>
</tbody>
</table>

*No observable respiratory effort and loss of capnographic waveform.

†Absence of upper airway (stridor, snoring) and breath sounds and loss of capnographic waveform.
Ketofol patients (41%) and 50 propofol patients (35%) received preprocedural analgesia. No patient received preprocedural analgesia within 30 minutes of the study protocol being initiated, and no unblinding envelopes were opened. All procedures were completed successfully, as determined by the treating physician.

In 1 ketofol sedation, oxygen was applied before the start of the sedation for a patient who developed chest pain while awaiting cardioversion. In 1 propofol sedation, a patient undergoing incision and drainage was administered midazolam to complete the procedure. No patient was hypoxic before the start of a procedure or after recovery from sedation. No patient had an unplanned prolonged (3 hours or more) ED stay or unplanned admission to the hospital.

The results of the blinding assessment were similar between the 2 groups, and there was no evidence to suggest unblinding. The range of correct guesses made by each sedation team member was 54% to 64% for the ketofol group (overall mean 58%) and 61% to 66% for the propofol group (overall mean 62%).

Main Results

The number and proportion of patients experiencing an adverse respiratory event were similar between the 2 groups, as was the distribution of respiratory events and interventions (Table 3).

Secondary outcomes are detailed in Table 4. Sedation consistency is also presented graphically in Figure 2, representing the percentage of time patients were at each sedation level during their procedures, and the need for repeated medication dosing during the procedure is represented graphically in Figure 3. Graphic presentation of each sedation interval is provided in Figure E1, available online at http://www.annemergmed.com.

Sedation efficacy was similar in the 2 groups. Of the 13 ketofol sedation events not considered efficacious, 8 were because of unpleasant recovery agitation and 3 were because of procedural agitation. Two patients had both procedural and recovery agitation. Of the 16 propofol sedations not considered efficacious, 14 were because of procedural agitation and 1 was because of rigidity. One patient had both rigidity and procedural agitation. Nonrespiratory adverse events were uncommon. Of the 5 patients experiencing procedural agitation in the ketofol group, 2 underwent incision and drainage, 2 underwent shoulder reduction, and 1 underwent wrist fracture reduction. Of the 15 patients experiencing procedural agitation in the propofol group, 8 underwent orthopedic fracture reductions and 7 underwent incision and drainage.

For physicians, median satisfaction score for ketofol was 10 (interquartile range [IQR] 8 to 10; range 3 to 10); for propofol, 9 (IQR 8 to 10; range 1 to 10). For nurses, median satisfaction scores were 10 for ketofol (IQR 10 to 10; range 1 to 10) and 9 for propofol (IQR 9 to 10; range 1 to 10). Patient-reported satisfaction with quality of sleep and procedural recall was a median of 10 for both the ketofol and the propofol groups.

LIMITATIONS

The use of the Quebec Criteria for reporting adverse events is limited by the fact that the decision to intervene is based on the judgment of the clinician. Different clinicians may have different intervention thresholds in the face of a potentially adverse event.
The variety of procedures performed had differing requirements for sedation and analgesia. The use of the same weight-based dosing schedule for procedures of varied painfulness may have affected the incidence of adverse events. However, the distribution of procedure types was similar between the 2 groups.

This study examined a single ratio of ketamine-propofol mixture and used a single weight-based dosing regimen. Adverse events may vary, depending on the ratio of ketamine and propofol used and on the rate of medication administration.

**DISCUSSION**

To our knowledge, this study is the largest reported randomized double-blind comparison of ketamine-propofol combination versus propofol alone for ED procedural sedation and analgesia. Using the

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**Table 3. Respiratory events and interventions.**

<table>
<thead>
<tr>
<th>Result</th>
<th>Ketofol, No. (%) [95% CI] (n=142)</th>
<th>Propofol, No. (%) [95% CI] (n=142)</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients experiencing a respiratory event</td>
<td>43 (30)[23 to 38]</td>
<td>46 (32)[25 to 41]</td>
<td>2 (−9 to 13)*</td>
</tr>
<tr>
<td><strong>Incidence of respiratory events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen desaturation</td>
<td>38 (27)[20 to 35]</td>
<td>36 (25)[19 to 33]</td>
<td>2 (−9 to 12)</td>
</tr>
<tr>
<td>Central apnea</td>
<td>15 (11)[7 to 17]</td>
<td>13 (9)[6 to 15]</td>
<td>2 (−5 to 9)</td>
</tr>
<tr>
<td>Partial upper airway obstruction</td>
<td>11 (8)[4 to 13]</td>
<td>11 (8)[4 to 13]</td>
<td>0</td>
</tr>
<tr>
<td>Complete upper airway obstruction</td>
<td>6 (4)[2 to 9]</td>
<td>4 (3)[1 to 7]</td>
<td>1 (−3 to 6)</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary aspiration</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory interventions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation/airway repositioning</td>
<td>5 (4)[2 to 8]</td>
<td>14 (10)[6 to 16]</td>
<td>6 (0.4 to 13)</td>
</tr>
<tr>
<td>Stimulation/airway repositioning plus oxygen</td>
<td>35 (25)[18 to 32]</td>
<td>31 (22)[16 to 29]</td>
<td>3 (−7 to 13)</td>
</tr>
<tr>
<td>Stimulation/airway repositioning, oxygen, plus bag-valve-mask</td>
<td>3 (2)[0.7 to 6]</td>
<td>1 (1)[0.1 to 4]</td>
<td>1 (−2 to 5)</td>
</tr>
</tbody>
</table>

*P=.80.
†Some patients had more than 1 event.
‡No patients received oral airway placement or endotracheal intubation.

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**Table 4. Secondary outcomes.**

<table>
<thead>
<tr>
<th>Sedation consistency</th>
<th>Ketofol (n=142) No. (%) [95% CI]</th>
<th>Propofol (n=142) No. (%) [95% CI]</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with RSS &lt;5 during procedure or requiring repeated dose during procedure</td>
<td>65 (46)[38 to 54]</td>
<td>93 (65)[57 to 73]</td>
<td>19 (8 to 31)*</td>
</tr>
<tr>
<td>Patients with RSS &lt;5 during procedure†</td>
<td>52 (37)[29 to 45]</td>
<td>75 (53)[45 to 61]</td>
<td>16 (5 to 27)</td>
</tr>
<tr>
<td>Patients requiring repeated dosing during procedure§</td>
<td>28 (20)[15 to 28]</td>
<td>63 (44)[36 to 52]</td>
<td>24 (12 to 33)</td>
</tr>
<tr>
<td>Efficacious sedation</td>
<td>129 (91)[85 to 95]</td>
<td>126 (89)[83 to 93]</td>
<td>2 (−5 to 9)</td>
</tr>
<tr>
<td>Procedural agitation</td>
<td>5 (3.5)[1.6 to 8.0]</td>
<td>15 (11.0)[6.5 to 16.7]</td>
<td>7.5 (1 to 14)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>1 (0.7)[0.2 to 3.8]</td>
<td>0.7 (−2 to 4)</td>
</tr>
<tr>
<td>Muscular rigidity</td>
<td>0</td>
<td>2 (1)[0.2 to 4.4]</td>
<td>1 (−1 to 5)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (0.7)[0.2 to 3.8]</td>
<td>0</td>
<td>0.7 (−2 to 4)</td>
</tr>
<tr>
<td>Recovery agitation receiving treatment</td>
<td>6 (4)[2.0 to 8.9]</td>
<td>0</td>
<td>4 (0.8 to 9)</td>
</tr>
<tr>
<td>Recovery agitation no treatment</td>
<td>4 (3)[1.1 to 7.0]</td>
<td>0</td>
<td>3 (−0.3 to 7)</td>
</tr>
</tbody>
</table>

**Median (IQR) [range]**

<table>
<thead>
<tr>
<th>Induction time*</th>
<th>Ketofol (n=142) Median (IQR) [range]</th>
<th>Propofol (n=142) Median (IQR) [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to RSS 5, min</td>
<td>2 (1 to 3)[1 to 6]</td>
<td>2 (1 to 3)[1 to 10]</td>
</tr>
<tr>
<td>Total doses required to reach RSS 5, No.</td>
<td>2 (2 to 3)[1 to 7]</td>
<td>2 (1 to 3)[1 to 9]</td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>4 (2 to 7)[1 to 28]</td>
<td>5 (2 to 7)[1 to 13]</td>
</tr>
<tr>
<td>Sedation time, min</td>
<td>7 (4 to 9)[1 to 29]</td>
<td>7 (4 to 9)[1 to 18]</td>
</tr>
<tr>
<td>Recovery time, min</td>
<td>8 (7 to 10)[1 to 26]</td>
<td>6 (2 to 8)[2 to 13]</td>
</tr>
<tr>
<td><strong>Total medication dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine and propofol, mg/kg each</td>
<td>0.7 (0.6 to 0.9)[0.4 to 1.6]</td>
<td>1.5 (1.1 to 2.0)[0.7 to 5.1]</td>
</tr>
<tr>
<td>Ketamine and propofol, mL/kg each</td>
<td>0.14 (0.12 to 0.18)[0.08 to 0.32]</td>
<td>0.15 (0.11 to 0.20)[0.07 to 0.51]</td>
</tr>
</tbody>
</table>

**RSS, Ramsay Sedation Score.**

*P<.001.
†Some patients had both RSS less than 5 and repeated dosing.
‡In 5 ketofol and 13 propofol subjects, the procedure began before RSS 5 was reached. In these cases, procedure start time was used to calculate induction time.
No patient experienced vomiting, bradycardia, or reversal agent use or had an unplanned hospital admission.
widely accepted intervention-based Quebec Criteria,\textsuperscript{33} we found that, when targeting deep sedation, the incidence of adverse respiratory events is not lessened when a 1:1 single-syringe mixture of ketamine and propofol is used compared with using propofol alone.

Ketamine is known to preserve respiratory function\textsuperscript{37}; thus, it has been theorized that the use of ketamine and propofol in combination may counterbalance the respiratory depression associated with propofol sedation.\textsuperscript{16} 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\textsuperscript{18,39} because it is known that the incidence of respiratory adverse events is associated with both the total dose and the rate of administration of propofol.\textsuperscript{6-8}

Propofol-alone sedation is commonly performed with an initial bolus of 1 mg/kg, followed by 0.5 mg/kg boluses every 3 minutes as necessary.\textsuperscript{40} The incidence of hypoxia and assisted ventilation has been reported to be from 8%\textsuperscript{41} to 14%.\textsuperscript{42} Some researchers have suggested that smaller initial and subsequent doses and slower administration of the initial dose during 60 seconds appear to lead to less oversedation and fewer respiratory adverse events. Bell et al\textsuperscript{43} used an initial dose of 0.5 to 1.0 mg/kg (mean of 0.8 mg/kg) of propofol, with subsequent 10- to 40-mg boluses as necessary. With this regimen, 123 of 400 patients (31%) required some type of airway intervention, with 2.7% and 2.2% of patients experiencing hypoxia and assisted ventilation, respectively. Zed et al\textsuperscript{44} used a propofol dosing regimen of 0.25 to 0.5 mg/kg of propofol as an initial dose during 60 seconds, followed by 10- to 20-mg boluses administered during 60 seconds each. None of the 113 patients in this study experienced apnea, and 1 patient developed oxygen desaturation below 90%. However, this relatively conservative dosing strategy resulted in a 5.8-minute (SD 3.6-minute) time to achieve the desired depth of sedation.

It is possible that the relatively rapid dosing regimen used in this study (every 1 minute, rather than the commonly used every 3-minute schedule\textsuperscript{40}) offset any protective effect provided by the reduction in total propofol dosage. Alternatively, it may be that such a protective effect does not exist. It is known that rapid intravenous infusion of ketamine has the potential to cause apnea.\textsuperscript{5} When comparing ketamine with propofol for moderate sedation, Miner et al\textsuperscript{45} found the surprising result that a larger proportion of adults receiving ketamine alone displayed signs of subclinical respiratory depression. However, this finding may have been confounded because supplemental oxygen was more commonly used in propofol patients compared with ketamine patients.

We found that deep sedation is reliably achieved with both ketofol and propofol. Despite the differing mechanisms of action of the 2 drugs, the time and the number of doses required to achieve deep sedation were similar for both regimens. When propofol alone is used, deep sedation can be achieved with doses of 1 to 2 mg/kg,\textsuperscript{45,46} whereas dissociative sedation with ketamine monotherapy usually requires 1.0 to 1.5 mg/kg.\textsuperscript{47} In our study, ketofol deep sedation was reliably achieved with approximately half of the dosage requirements of each drug (0.7 mg/kg; IQR 0.55 to 0.90 mg/kg), which is consistent with previous reports of ketofol usage in adults.\textsuperscript{42,25}
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REFERENCES


It has been previously reported that ketofol procedural sedation results in more consistent depth of sedation compared with propofol sedation, despite the decreased amount of propofol used with ketofol. These observations are supported by our findings because fewer patients in the ketofol group required repeated dosing to maintain deep sedation, and fewer ketofol patients progressed to a Ramsay Sedation Score of 4 or less during their procedures. These findings support the hypothesis that the use of ketamine in combination with propofol provides a sedative effect that blunts the erratic peaks and troughs of propofol monotherapy.

There was a higher incidence of agitation during the procedure in the propofol group compared with the ketofol group. These events appear to have occurred during procedures known to be significantly painful. When performing painful ED procedures such as fracture reduction and incision and drainage of abscesses, many clinicians choose to use opioid analgesia during procedural sedation. Because it is known that ketamine provides analgesia during propofol sedation with fewer adverse airway events compared with fentanyl or alfentanil, ketamine is considered by some to be a logical choice as an analgesic medication during procedural sedation. However, the provision of preemptive analgesia is controversial because the clinical significance of brief painful stimuli is not known. Further studies would be necessary to determine whether the analgesic effect of ketamine results in a reduction in patient agitation and combativeness during painful procedures compared with propofol alone.

Agitation during the recovery phase was more common in the ketofol group, a finding that was anticipated because of previous publications. The incidence of problematic recovery agitation in adults receiving ketamine is estimated to be between 10% and 20%. The sedative effects of propofol are thought to blunt the recovery agitation observed with ketamine sedation. In this study, recovery agitation occurred less frequently than expected according to these previous findings, with only 6 patients (4%; 95% CI 2.0% to 8.9%) requiring treatment with midazolam after receiving ketofol sedation.

In our study, the incidence of other nonrespiratory adverse events was low in both groups. Ketamine is known to cause nausea and vomiting, the incidence of which is estimated to be between 5% and 15% in adults. This effect appears to be mitigated by the antiemetic activity of propofol, which has been found to be comparable to that of ondansetron when combined with ketamine sedation.

Our secondary findings should be viewed as hypothesis generating but may provide support for the concept of synergy between ketamine and propofol in terms of dosing requirements and nonrespiratory adverse effects when used in combination for ED procedural sedation and analgesia. Pending further research on optimal medication ratios and dosing schedules, these findings may assist clinicians choosing appropriate sedation regimens for patients and procedures that have various requirements for sedation and analgesia.

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Table E1. Ramsay Sedation Score.

<table>
<thead>
<tr>
<th>Score</th>
<th>Patient Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious or restless or both</td>
</tr>
<tr>
<td>2</td>
<td>Cooperative, orientated and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Asleep - responds quickly to normal voice commands</td>
</tr>
<tr>
<td>4</td>
<td>Asleep - no response to normal voice - brisk response to loud voice, or light forehead tap</td>
</tr>
<tr>
<td>5</td>
<td>Asleep-no response to above – shows sluggish response to loud voice or light forehead tap</td>
</tr>
<tr>
<td>6</td>
<td>Asleep – no response to loud voice or forehead tap – sluggish purposeful response to pain only</td>
</tr>
<tr>
<td>7</td>
<td>Reflex withdrawal (not purposeful) to pain only</td>
</tr>
<tr>
<td>8</td>
<td>No response, even to pain</td>
</tr>
</tbody>
</table>

Parameter 0 1 2
Level of consciousness/sedation Nonresponsive, or responsive only to painful stimuli Responds to verbal stimuli but falls asleep readily Awake and orientated (child oriented to parent), or equivalent to preoperative status
Circulation Systolic BP <100 mm Hg Systolic BP >100 mm Hg Systolic BP within normal limits for patient
Respiration Apneic: requires airway support Shallow, irregular breathing Able to breathe deeply and cough on command or equivalent to preoperative status
Oxygen saturation SpO₂ ≤92% on oxygen SpO₂ >92% on oxygen SpO₂ ≥94% on oxygen or equivalent to preoperative status
Activity level Unable to lift head or move extremities voluntarily or on command Lifts head or moves extremities on command Lifts head and moves all extremities spontaneously. Is able to ambulate consistent with surgical procedure or equivalent to preoperative status.

*Recovery criteria: minimum score of 8, with a minimum of 2 in respiratory and oxygen saturation.

Table E2. Modified Aldrete Scale.*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness/sedation</td>
<td>Nonresponsive, or responsive only to painful stimuli</td>
<td>Responds to verbal stimuli but falls asleep readily</td>
<td>Awake and orientated (child oriented to parent), or equivalent to preoperative status</td>
</tr>
<tr>
<td>Circulation</td>
<td>Systolic BP &lt;100 mm Hg</td>
<td>Systolic BP &gt;100 mm Hg</td>
<td>Systolic BP within normal limits for patient</td>
</tr>
<tr>
<td>Respiration</td>
<td>Apneic: requires airway support</td>
<td>Shallow, irregular breathing</td>
<td>Able to breathe deeply and cough on command or equivalent to preoperative status</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>SpO₂ ≤92% on oxygen</td>
<td>SpO₂ &gt;92% on oxygen</td>
<td>SpO₂ ≥94% on oxygen or equivalent to preoperative status</td>
</tr>
</tbody>
</table>

SP0₂, Oxygen saturation; BP, blood pressure.
Figure E1. Sedation intervals. A, Induction time; B, procedure time; C, sedation time; and D, recovery time.