Propofol or Ketofol for Procedural Sedation and Analgesia in Emergency Medicine—The POKER Study: A Randomized Double-Blind Clinical Trial

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Study objective: We determine whether emergency physician–provided deep sedation with 1:1 ketofol versus propofol results in fewer adverse respiratory events requiring physician intervention when used for procedural sedation and analgesia.

Methods: Consenting patients requiring deep sedation were randomized to receive either ketofol or propofol in a double-blind fashion according to a weight-based dosing schedule. The primary outcome was the occurrence of a respiratory adverse event (desaturation, apnea, or hypoventilation) requiring an intervention by the sedating physician. Secondary outcomes included hypotension and patient satisfaction.

Results: Five hundred seventy-three patients were enrolled and randomized, 292 in the propofol group and 281 in the ketofol group. Five percent in the propofol group and 3% in the ketofol group met the primary outcome, an absolute difference of 2% (95% confidence interval [CI] −2% to 5%). Patients receiving propofol were more likely to become hypotensive (8 versus 1%; difference 7%; 95% CI 4% to 10%). Patient satisfaction was very high in both groups (10/10; interquartile range 10 to 10/10), and although the ketofol group was more likely to experience severe emergence delirium (5% versus 2%; difference 3%; 95% CI 0.4% to 6%), they had lower pain scores at 30 minutes postprocedure. Other secondary outcomes were similar between groups.

Conclusion: Ketofol and propofol resulted in a similar incidence of adverse respiratory events requiring the intervention of the sedating physician. Although propofol resulted in more hypotension, the clinical relevance of this is questionable, and both agents are associated with high levels of patient satisfaction. [Ann Emerg Med. 2016;■:1-9.]

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INTRODUCTION

Background

The performance of noxious procedures is frequently required in emergency departments (EDs), and procedural sedation and analgesia is often used to facilitate these in a humane and effective manner.[1,2] The competent provision of safe and adequate procedural sedation is a core skill of an emergency physician.

Propofol and ketamine are commonly used as sedative agents in emergency medicine, and each has advantages and disadvantages. Propofol is associated with hypotension, loss of airway reflexes, hypoventilation, apnea, and hypoxia[3,4] but has antiemetic and amnestic properties.[5] Ketamine causes hypertension and tachycardia, as well as vomiting and emergence delirium,[6] but is associated with maintained airway reflexes and is a potent analgesic.[6-8]

It has been demonstrated that ketofol is effective for ED procedural sedation and analgesia,[9-12] and it has been hypothesized that its use results in fewer adverse events during sedation than when propofol is used alone, as a result of a lower overall dose of each drug being necessary and a "balancing" of their effects.[13,14] Despite these theoretical advantages of ketofol, previous single-center randomized controlled trials have not shown a reduction in respiratory adverse events.[15-17]

Importance

The combination of ketamine and propofol in a 1:1 ratio in a single syringe may provide effective procedural sedation and analgesia, with a lower incidence of adverse events requiring intervention, than when propofol is used alone.

Editor's Capsule Summary

What is already known on this topic

Previous randomized controlled trials have failed to confirm anecdotal claims of superiority of the combination "ketofol" over propofol alone for adult emergency department procedural sedation.

What question this study addressed

Is there a difference in the frequency of airway and respiratory adverse events between 1:1 ketofol and propofol alone?

What this study adds to our knowledge

Respiratory adverse events were similar between groups in this 573-patient controlled trial. The authors' preplanned secondary and additional exploratory outcomes revealed no clinically important advantages to ketofol.

How this is relevant to clinical practice

This largest-ever trial confirms earlier rigorous controlled trials that identified no clinically relevant benefit from adding ketamine to propofol for procedural sedation. Such findings are common outcomes when rigorous study is conducted of typically positive and enthusiastic early reports for many interventions.

Goals of This Investigation

This study aimed to determine whether propofol and ketamine mixed in a single syringe in a 1:1 ratio resulted in fewer adverse respiratory events (defined as a change in respiratory physiology, combined with the need for intervention, according to the Quebec criteria[18]) than propofol as a single agent. In addition, we also sought to determine whether there was a difference in rates of hypotension and patient satisfaction with one sedative agent compared with the other.

MATERIALS AND METHODS

Study Design and Setting

This was a randomized, double-blind clinical trial approved by the Human Research and Ethics Committees of South West Sydney Area Health Service and Metro South, Queensland. The study was registered with the Australia New Zealand Clinical Trials Registry. The study was performed between April 2013 and April 2015 at Bundaberg Base Hospital (a mixed rural regional hospital with an annual ED census of 50,000), Queen Elizabeth II Memorial Hospital (a mixed urban district hospital with an annual ED census of 60,000), and Liverpool Hospital (a mixed tertiary hospital with an annual ED census of 76,000). Each department is led by Fellows of the Australasian College for Emergency Medicine (FACEM), with additional medical staffing provided by general medical trainees (postgraduate years 1 and 2), training and nontraining registrars in emergency medicine, and non-FACEM senior physicians.

Registrars, FACEMs, and non-FACEM senior physicians were trained in the study protocol and involved in recruitment and conduct of the trial.

Selection of Participants

We enrolled eligible patients aged 18 years or older who, in the opinion of the treating emergency physician, required deep procedural sedation to facilitate the performance of a painful procedure in the ED. Patients were excluded if they were unable to provide informed consent; were pregnant; were allergic to ketamine, soy products, or eggs; had a reduced level of consciousness or known raised intracranial pressure; had uncontrolled hypertension (blood pressure >160/90 mm Hg), abdominal aortic aneurysm, or symptomatic ischemic heart disease; had heart failure or recent myocardial infarction; or had other severe systemic disease (American Society of Anaesthesiologists class IV or greater).

Consistent with usual departmental practice, titrated intravenous opiates were encouraged for patients with painful conditions (eg, fractures) before randomization, although no specific washout period was recommended between opiate administration and the commencement of sedation. All sedations occurred in the resuscitation room, with continuous cardiac monitoring, pulse oximetry, and waveform capnography, with noninvasive blood pressure and Wisconsin Sedation Scale score measured every 3 minutes. Administration of prophylactic oxygen was at the discretion of the treating physician.

Minimum staffing consisted of a registered nurse and 2 physicians, one to provide sedation and the other to perform the procedure.

Randomization occurred in blocks of 4, using a Web-based randomization program (http://sealedenvelope.com). Study packs were compiled in advance according to the randomization sequence and included a case report form and a prescription for the randomized medication. These were stored in a designated area of each department, and after the provision of informed consent, the next pack in the sequence was selected by a nurse and physician otherwise uninvolved in the study. These staff members opened the pack and drew up the study medication in an

area of the department remote to the sedation, according to the prescription contained within. The study medication was either "ketofol," consisting of ketamine 100 mg in 10 mL and propofol 100 mg in 10 mL, or propofol 200 mg in 20 mL. A syringe containing 20 mL of opaque white liquid and labeled as "study drug" was then provided to the sedating physician, who was blinded to its contents, as were the patient, procedural physician, and registered nurse present for the procedure.

Interventions

Patients received the study drug in titrated aliquots according to a weight-based dosing schedule (Table E1, available online at http://www.annemergmed.com). After the initial bolus of 0.05 mL/kg, additional aliquots of 0.025 mL/kg were given no more frequently than every 60 seconds at the discretion of the sedating physician. The procedure commenced when the sedating physician believed that an adequate depth of sedation had been achieved (routinely until the patient had his or her eyes closed and was unresponsive to verbal stimuli).

Vital signs and depth of sedation were recorded on the case report form every 3 minutes by the registered nurse (Table E2, available online at http://www.annemergmed.com), and recording continued until completion of the procedure and the reestablishment of clear verbal contact with the patient.

If more than 20 mL of study medication was required, open-label 1% propofol was used.

After recovery, patients were monitored for recovery agitation, and 30 minutes after the reestablishment of verbal contact, a brief questionnaire was administered by the registered nurse or sedating physician, inquiring about patient satisfaction, pain score, procedural recall, and recollection of any hallucinations.

Data Collection and Processing

Data collection was performed by either the sedating physician or registered nurse, and data were entered on printed case report forms separate from the clinical record. Because all the data points from the departments' standard procedural sedation forms were included, dual data entry was not required. Before sedation, demographic data, medical history, current medications, airway assessment, fasting status, and pain score (0 to 10) were recorded, as were medications administered within the hour before the procedure.

The occurrence of adverse events and interventions, as well as procedural success, was recorded prospectively by means of check boxes. If the procedure was unsuccessful, the sedating physician's opinion about whether this was due to sedative or procedural issues was recorded by means of a check box.

Intraprocedural conduct of the patient was recorded by check boxes as compliance/still, mild agitation, interference with the procedure, or procedure failure.

The duration of the procedure and sedation was recorded as the procedure commencement subtracted from the procedure end time.

Patients were monitored for emergence delirium according to their maximum ED procedural sedation Emergence Delirium Score (Table E3, available online at http://www.annemergmed.com). From this information, post hoc, patients were divided into experiencing no, mild, or unpleasant emergence delirium.

Thirty minutes after the reestablishment of verbal contact, patients were interviewed about their pain level during the procedure and currently (0=no pain, 10=worst pain imaginable), satisfaction with the sedation (0=completely dissatisfied, 10=completely satisfied), and recall of the procedure (0=none, 10=total recall). They were also asked about the presence of hallucinations and, if present, whether they were pleasant, unpleasant, or neither. A free-text description of any hallucinations was also sought.

The time that patients reached a total score of greater than or equal to 7 on the discharge key (Table E4, available online at http://www.annemergmed.com) was also recorded.

Data were entered in Microsoft Excel (version 2015; Microsoft, Redmond, WA) for tabulation by a single researcher (L.N.), who was uninvolved in subject recruitment or sedation, and then imported into Stata (version 11.0; StataCorp, College Station, TX) for analysis.

Outcome Measures

Our primary outcome measure was the occurrence of a respiratory event, defined as hypoxia (SpO_2 $\leq$93%), hypoventilation (respiratory rate $\leq$8 breaths/min), apnea (no capnography trace for $\geq$15 seconds), laryngospasm or aspiration (persistent hypoxia plus infiltrates on chest radiograph), and the occurrence of a rescue intervention (increased oxygen flow rate, airway repositioning/opening, use of an airway adjunct, bag-valve-mask ventilation, or intubation), according to the Quebec criteria.[18] Although the Quebec criteria also include vigorous tactile stimulation, it was thought that including this would add confusion because it is also frequently used to assess the depth of sedation, rather than purely as a rescue intervention.

Secondary outcomes included hypotension (systolic blood pressure <90 mm Hg) and patient satisfaction; in addition, we also evaluated exploratory outcomes of vomiting, aspiration (hypoxia and new aspirates on chest radiography), median sedative dose, median duration of

sedation, occurrence of emergence delirium, patient recollection and pain scoring, and clinician satisfaction.

Primary Data Analysis

The study was powered to demonstrate a reduction in our primary endpoint from 20% to 10%, suggesting a required sample size of 526 (263 in each arm), with a level of significance set at 95% (α error 5%), with power at 90% (β error 10%), using a 2-sided test. Approximately 10% was added to enrollment to offset potential dropouts.

The anticipated adverse event rate used to inform the power calculation was derived from a 2-year, multicenter study of sedation practices in Australasian EDs,[19] with the anticipated rate for ketofol being based on a large prospective case series reported by Willman et al.[9]

Analysis was by intention to treat. Categorical variables were reported as percentages with 95% confidence intervals (CIs) and were analyzed with the χ^2 test or Fisher's exact test. CIs for the difference between ordinal values were calculated with the Hodges-Lehmann estimator.

RESULTS

Characteristics of Study Subjects

A total of 573 patients were recruited across the 3 study sites, with 281 in the ketofol group and 292 in the propofol group. Data were available for the primary outcome on all of the patients enrolled.

An additional 467 patients were screened for inclusion but not enrolled (Figure). A total of 14 patients were excluded after randomization because they either met exclusion criteria (most frequently hypertension) or were not sedated as part of the study for other reasons (Figure).

The 2 groups were similar at baseline in terms of their characteristics and procedures undertaken (Table 1), as well as in the volume of study drug used (both groups=10.8 mL; 95% CI 9.9 to 11.8 mL).

As is common procedural sedation practice in Australian EDs, prophylactic oxygen use was almost universal, with similar flow rates in both arms (Table 1). Use of preprocedural opiates was also similar, although consistent with a protocol that encouraged titrated opiate use before randomization; the majority of patients did not receive these within the hour before their procedure (Table 1).

Main Results

The occurrence of the primary endpoint was similar in the propofol and ketofol groups. When the constituents of the primary endpoint were considered individually, again they were similar in both groups, with the exception of bag-valve-mask ventilation, which occurred more frequently in the propofol group (Table 2).

Hypotension was more common in the propofol group (Table 3), with a systolic blood pressure of less than 90 mm Hg being recorded in 7% of the propofol group compared with only 1% of the ketofol group. However, although this was statistically significant ($P>.0001$), it did not require any intervention beyond a fluid bolus, and so the clinical significance of this finding is doubtful.

Patient satisfaction was high with both agents, with similar distribution of satisfaction scores between groups.

Both groups had high levels of procedural success, with only 1 patient (in the propofol group) not having the procedure completed for reasons related to the sedation. Minor agitation (manifesting as procedural interference but not procedural failure) during the procedure was more likely to occur in patients receiving propofol than in those sedated with ketofol (Table 4).

Patients receiving ketofol were more likely to experience emergence delirium and hallucinations, although in the majority of cases, these were minor phenomena and, in the case of hallucinations, usually described as pleasant (Table 4).

Pain scores at 30 minutes postprocedure were lower in the ketofol group (Table 4), although this did not appear to affect patient satisfaction.

Depth of sedation was similar in both groups (Table 5). However, at the 6- and 9-minute points, the median sedation scores were lower with ketofol, possibly as a function of the analgesic properties of ketamine, although this was not statistically significant. However, because this is likely to encompass the time during an ED procedure during which a noxious stimulus is applied, there may be some relevance to this finding.

Finally, the mean time to reach a discharge key score of 7 or more was longer in the ketofol group (Table 4).

LIMITATIONS

Our study, although large, had some limitations. We recruited a convenience sample; selection bias may have occurred because of this, as well as because of staffing limitations, which made recruitment less likely at times of peak departmental activity, as well as overnight, because it was mandated in our study that a consultant emergency physician be present within the department to supervise the sedation.

Preparation of the study medication occurred within the same department as the conduct of the study. This occurred because ketofol's stability as a mixture has only been established as lasting for 3 hours,[20] and because of restrictions in regard to dangerous-drug laws in Australia.

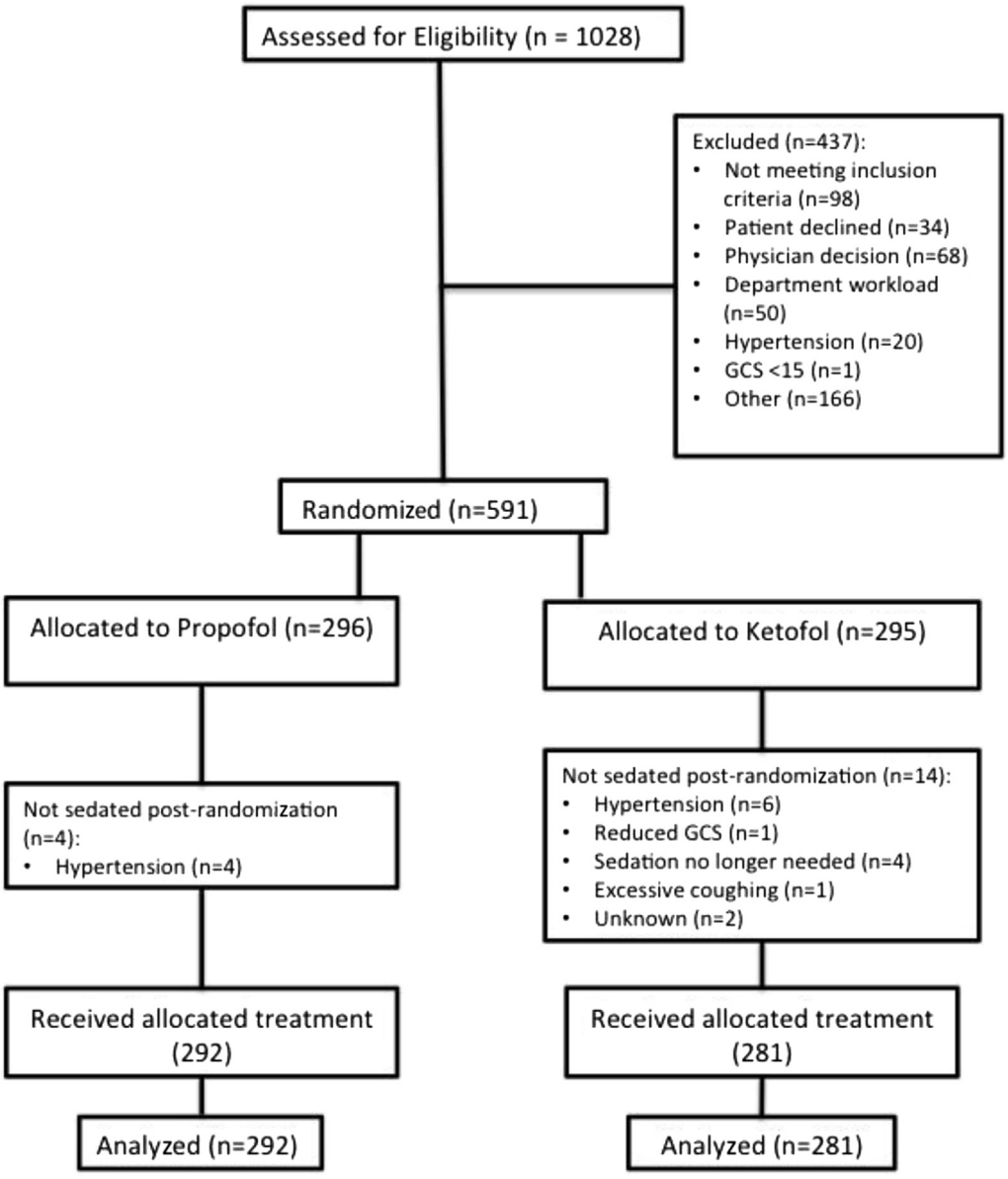

Figure. Flow of study subjects.

Although unavoidable, this proximity could have resulted in some unblinding.

Our decision not to control for prophylactic oxygen delivery or preprocedural opiate use may have also introduced confounders into the study.

The final limitation is the use of a combined physiologic- and intervention-based outcome measure, which involves an element of subjectivity because different physicians may have different triggers that cause them to intervene.

DISCUSSION

To the best of our knowledge, ours is the largest study to compare ketofol in a 1:1 ratio in a single syringe with equivalent volumes of 1% propofol for ED procedural sedation and analgesia.

Consistent with previous work, our study showed a similar incidence of airway and respiratory events requiring intervention in both arms. We had defined a priori a 10% difference in the incidence of respiratory complications requiring physician intervention as being clinically significant; both the point estimate and upper limit of the 95% CI were less than this, and so we concluded that we did not miss a clinically important difference in this regard. There were no serious adverse events in either arm, and therefore we believe that both options are similarly safe. Given the consistency of these findings between our study

Table 1. Characteristics of patients receiving intravenous ketofol or propofol.

	Propofol (292)	Ketofol (281)
Age, median (IQR), range, y	46 (30–62) 19–86	50 (31–65) 18–95
Sex		
Male, No. (%)	145 (49)	138 (49)
Weight, kg		
Median (IQR)	82 (69–96)	78 (68–91)
Range	40–147	44–150
Pain score before procedure, median (IQR)	5 (2–7)	4 (1–6)
Baseline systolic BP, median (IQR), mm Hg	132 (120–147)	137 (124–148)
Fasted ≥3 h, % (95% CI)	95 (92–98)	95 (92–98)
Procedure, No. (%)		
Upper limb fracture reduction	62 (21)	77 (28)
Lower limb fracture reduction	29 (10)	25 (9)
Abscess incision and drainage	59 (20)	57 (20)
Shoulder reduction	43 (15)	34 (12)
Other joint reduction	42 (14)	39 (14)
Cardioversion	25 (9)	27 (10)
Other indication	32 (11)	22 (8)
Comorbidities, No. (%)		
Ischemic heart disease	19 (6)	15 (5)
Hypertension	55 (19)	56 (20)
Diabetes mellitus	26 (9)	22 (8)
Epilepsy	3 (1)	4 (1)
Asthma	9 (3)	10 (4)
Prophylactic oxygen use, No. (%)	288 (98.6)	280 (99.6)
Oxygen flow rate (IQR), L/min	4 (2–6)	4 (3–6)
Morphine		
Patients receiving, No. (%)	46 (16)	61 (22)
Median dose (IQR), mg	5 (5–10)	5 (5–10)
Mean dose (95% CI), mg/kg	0.02 (0.01–0.03)	0.02 (0.02–0.04)
Fentanyl		
Patients receiving, No. (%)	33 (11)	30 (11)
Median dose (95% CI), mg/kg	50 (25–75)	75 (50–100)
Mean dose (95% CI), μg/kg	0.1 (0.06–0.13)	0.1 (0.06–0.14)
Study drug		
Dose administered, median (IQR), mL/kg	0.120 (0.05–0.21)	0.125 (0.07–0.19)
Propofol, median (IQR), mL/kg	1.3 (0.5–2.1)	0.675 (0.7 –1.9)
Ketamine, median (IQR), mL/kg	0	0.675 (0.7 –1.9)

IQR, Interquartile range.

Table 2. Primary outcome, with constituent outcomes.

	Propofol, No. (%), n=292	Ketofol, No. (%), n=281	Difference, % (95% CI)
Composite endpoint (occurrence of any respiratory event and intervention)	27 (9)	21 (7)	2 (–2 to 6)
Airway events			
Desaturation (SpO_2 ≤93%)	23 (8)	17 (6)	
Apnea (loss of $ETCO_2$ ≥15 s)	16 (5)	11 (4)	
Hypoventilation (RR ≤8)	13 (4)	3 (9)	
Airway obstruction	0	0	
Laryngospasm	0	0	
Aspiration	0	0	
Occurrence of any airway event	32 (10)	23 (8)	2 (–3 to 7)
Respiratory interventions			
Increased oxygen flow rate	15 (5)	12 (4)	
Airway repositioned/opened	34 (12)	27 (9)	
Airway adjunct use	2 (0.6)	1 (0.3)	
Bag-valve-mask use	9 (3)	3 (1)	
Occurrence of any respiratory intervention	47 (16)	38 (14)	2 (–3 to 7)

$ETCO_2$, End tidal CO_2.

and the work undertaken previously, we believe that this conclusion is definitive.

Our main secondary outcomes of hypotension and patient satisfaction are interesting. Although propofol results in more hypotension, this was universally self-limiting, and so although this difference was statistically significant, is of doubtful clinical significance. Patient satisfaction was high in both groups, with identical medians, interquartile ranges, and ranges, so despite more emergence delirium in the ketofol group, overall, patients were similarly satisfied with either agent.

Our other secondary outcomes can only be viewed as hypothesis generating, but they suggest some interesting differences between ketofol and propofol. Although the depth of sedation was similar in both arms, there was a minor trend to lower sedation scores with ketofol early in the sedation timeline, with the median sedation scores for ketamine at 6 and 9 minutes being a point lower on the Wisconsin Sedation Scale (although the 95% CI for the difference included zero); this minor trend appears consistent with that of other similar studies.[15-17] It seems plausible that when aiming for deep sedation, using one agent with analgesic properties and one without, sedation depth on a scale that includes painful stimulus would tend to be deeper with the analgesic agent. Possibly related to this analgesic effect, ketofol was associated with higher rates of intraprocedural compliance, with fewer patients becoming agitated during the procedure, which again is consistent with the randomized controlled trial by Andolfatto et al,[15] although Miner et al[16] did not observe the same. This may be an interesting direction for future research. Propofol and ketofol were both associated with some degree of emergence delirium in our study, although this was frequently minor. More severe emergence delirium was slightly more likely to occur with ketofol, although because the absolute difference was only 3% (95% CI 0.4% to 6%), the number needed to treat to avoid 1 episode would be 33 (95% CI 17 to 250). Pain scores at 30 minutes postprocedure were lower in the ketofol group, although this did not appear to affect patient satisfaction.

Table 3. Main secondary outcomes.

	Propofol (n=292)	Ketofol (n=281)	Difference (95% CI)
Hypotension (SBP ≤90 mm Hg), No. (%)	24 (8)	3 (1)	7 (4–10)
Patient satisfaction with sedation, median (IQR) [range]	10 (10–10) [0–10]	10 (10–10) [0–10]	0 (0–0)

Previous observational work[9-12] has shown that ketofol is effective for ED procedural sedation, and subsequent randomized controlled trials comparing ketofol with propofol[15-17] found no difference in primary outcomes. However, these have been single-center studies, recruiting smaller samples, and some key differences exist in regard to oxygen and opiate delivery. In their randomized controlled trial, Andolfatto et al[15] did not routinely use supplemental oxygen and mandated a washout period for opiates; Miner et al[16] included a washout period for opiates but routinely used prophylactic oxygen, whereas David and Shipp[17] used prophylactic oxygen at 2 L/minute and administered a fentanyl bolus 5 minutes before the commencement of sedation. Routine practice in our clinical environments is to use prophylactic oxygen at the discretion of the sedating physician, with no mandated washout period for opiates, and so the same approach was used in our study, although early use of titrated opiate analgesia led to relatively low opiate use within the hour before the procedure.

The multicenter nature of our study, and the fact that it was conducted in departments of differing size and case mix, increases the external validity of our findings and consolidates the results of previous work, helping to inform clinical practice.

The fact that our results were consistent with those of all of the previous randomized controlled trials, despite some methodological differences, particularly in regard to oxygen and opiate use, provides additional reassurance that these findings are true, rather than a result of chance.

Providers have typically been reluctant to use ketamine in adults because of concern about emergence phenomena, with rates of 10% to 20% being quoted in the literature.[21] The rates of unpleasant emergence delirium (defined as an Emergency Department Procedural Sedation Emergence Delirium scale score ≥4) in our study were lower than this (6%; 95% CI 3% to 9%), suggesting that in this regimen, one of the adverse events most likely to deter providers from the use of ketamine is less likely to occur with ketofol than when ketamine is used as a single agent. A previous randomized controlled trial by Sener et al[22] showed a similar reduction in emergence phenomena when midazolam was combined with ketamine in adults, whereas Shah et al[23] compared ketofol and ketamine in children, again observing less emergence delirium with coadministration.

Our results appear to be consistent with this previous work in showing that the combination use with propofol can ameliorate this occasionally distressing effect of ketamine.

Table 4. Exploratory secondary outcomes.

	Propofol, No. (%) [95% CI], n=292	Ketofol, No. (%) [95% CI], n=281	Difference, % (95% CI)
Mild agitation	59 (20)	33 (12)	8 (2 to 14)
Procedural interference	13 (4)	6 (2)	2 (–0.5 to 5)
Procedural failure	1 (0.3)	0	1 (–0.1 to 2)
Vomiting	8 (3)	12 (4)	1 (–0.1 to 8)
Hallucinations (all)	46 (15)	100 (35)	20 (13 to 27)
Pleasant	28 (10)	70 (25)	15 (9 to 21)
Unpleasant	3 (1)	8 (3)	2 (–0.2 to 4)
Emergence delirium (any)*	59 (20)	77 (27)	7 (4 to 10)
Minor	54 (18)	63 (22)	4 (–3 to 10)
Severe	5 (2)	14 (5)	3 (0.4 to 6)
Time from sedation to DKS ≥7, min Mean (95% CI)	24 (22 to 26)	33 (29 to 37)	9 (7 to 11)
Recall of procedure, median (IQR) [range]	0 (0 to 0) [0 to 10]	0 (0 to 0) [0 to 10]	0 (0 to 0)
Maximal pain during procedure, median (IQR) [range]	0 [0 to 0] [0 to 9]	0 (0 to 0) [0 to 10]	0 (0 to 0)
Pain score 30 min postprocedure, median (IQR) [range]	3 (0 to 5) [0 to 10]	0 (0 to 3) [0 to 10]	3 (2 to 3)
Patient satisfaction with procedure, median (IQR) [range]	10 (10 to 10) [10 to 10]	10 (10 to 10) [10 to 10]	0 (0 to 0)

*Minor emergence delirium=repetitive talking but calm, calm hallucinations or double vision, and interaction with caregivers but not distressed. Severe emergence delirium=restless, cries occasionally, inconsolable, thrashing about, or requiring medication to settle because of excessive combativeness or agitation.

Table 5. Depth of sedation (Wisconsin Sedation Scale score) and duration of sedation.

Time, Minutes	Propofol, Median (IQR)	n	Ketofol, Median (IQR)	n	Difference (95% CI)
0	5 (5–5)	292	5 (5–5)	281	0 (0–0)
3	3 (2–4)	292	3 (1–4)	281	0 (0–0)
6	3 (1–4)	217	2 (1–4)	224	1 (0–1)
9	3 (1–4)	201	2 (1–4)	213	1 (0–1)
12	3 (2–4)	178	4 (2–4)	185	0 (0–0)
15	4 (2–5)	138	4 (2–5)	155	0 (0–1)
18	4 (3–5)	102	4 (3–5)	120	0 (0–0)
21	5 (3–5)	83	4 (4–5)	89	0 (0–0)
24	5 (3–5)	64	5 (4–5)	70	0 (0–0)
27	5 (3–5)	49	5 (4–5)	63	0 (0–0)
30	5 (3–5)	34	5 (4–5)	53	0 (0–0)
33	5 (4–5)	28	5 (4–5)	47	0 (0–0)
36	5 (3–5)	25	5 (5–5)	41	0 (0–0)
39	5 (3–5)	23	5 (3–5)	33	0 (0–0)

Our data revealed shorter recovery times with propofol, although the reduction was by a median of only 9 minutes. Although this may not be significant from the perspective of the individual patient, it may be an important consideration in a busy ED, particularly with respect to the length of time that a resuscitation bed is occupied, despite the fact that the duration of sedation is often not the rate-limiting step with regard to eventual discharge readiness.

In conclusion, adult procedural sedation using ketofol versus propofol alone results in similar frequency of adverse respiratory events requiring intervention. Propofol was associated with a slightly higher incidence of hypotension, which is of doubtful clinical consequence, and patients were highly satisfied with both agents.

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Table E1. Weight-based dosing schedule.

Patient Weight, kg	Initial Bolus, mL	Subsequent Boluses, mL
<50	2.5	1.5
50–59	3	1.5
60–69	3.5	2
70–79	4	2
80–89	4.5	2.5
≥90	5	2.5

Table E2. Wisconsin Sedation Scale score.

Anxious, agitated, or in pain	6
Spontaneously awake without stimulus	5
Drowsy, eyes open or closed, but easily rouses to consciousness with verbal stimulus	4
Arouses to consciousness with moderate tactile or loud verbal stimulus	3
Arouses slowly to consciousness with sustained painful stimulus	2
Arouses, but not to consciousness, with painful stimulus	1
Unresponsive to painful stimulus	0

Table E3. ED procedural sedation emergence delirium score, with post hoc grouping.

Score	Description	Post Hoc Grouping
0	No emergence delirium	No emergence delirium
1	Repetitive talking, but calm	Mild/pleasant emergence delirium
2	Calm hallucinations/double vision	
3	Interacting with caregivers, not distressed	
4	Restless, cries occasionally	Severe/unpleasant emergence delirium
5	Inconsolable, thrashing about	
6	Requiring medication	

Table E4. Discharge key score.

Musculoskeletal		Respiratory	
Inability to lift head or move extremities on command	0	Apneic	0
Lifts head spontaneously, or moves extremities voluntarily or on command	1	Dyspnea, or shallow, irregular breathing	1
Able to ambulate without assistance	2	Able to breathe deeply or cough on command	2
Neurologic		**Cardiovascular**	
Not responding, or responding only to painful stimuli	0	Systolic BP <80 mm Hg	0
Responds to verbal stimuli but falls asleep readily	1	Systolic BP >80 and <100 mm Hg	1
Awake, alert, orientated to time, place, and person	2	Systolic BP normal for patient	2