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PROGRESSIVE CLINICAL PRACTICE

Incidence of Adverse Events in Adults Undergoing Procedural Sedation in the Emergency Department: A Systematic Review and Meta-analysis

M. Fernanda Bellolio, MD, MS, Waqas I. Gilani, MD, Patricia Barrionuevo, MD, M. Hassan Murad, MD, MPH, Patricia J. Erwin, MLS, Joel R. Anderson, James R. Miner, MD, and Erik P. Hess, MD, MSc

Abstract

Objectives: This was a systematic review and meta-analysis to evaluate the incidence of adverse events in adults undergoing procedural sedation in the emergency department (ED).

Methods: Eight electronic databases were searched, including MEDLINE, EMBASE, EBSCO, CINAHL, CENTRAL, Cochrane Database of Systematic Reviews, Web of Science, and Scopus, from January 2005 through 2015. Randomized controlled trials and observational studies of adults undergoing procedural sedation in the ED that reported a priori selected outcomes and adverse events were included. Meta-analysis was performed using a random-effects model and reported as incidence rates with 95% confidence intervals (CIs).

Results: The search yielded 2,046 titles for review. Fifty-five articles were eligible, including 9,652 procedural sedations. The most common adverse event was hypoxia, with an incidence of 40.2 per 1,000 sedations (95% CI = 32.5 to 47.9), followed by vomiting with 16.4 per 1,000 sedations (95% CI = 9.7 to 23.0) and hypotension with 15.2 per 1,000 sedations (95% CI = 10.7 to 19.7). Severe adverse events requiring emergent medical intervention were rare, with one case of aspiration in 2,370 sedations (1.2 per 1,000), one case of laryngospasm in 883 sedations (4.2 per 1,000), and two intubations in 3,636 sedations (1.6 per 1,000). The incidence of agitation and vomiting were higher with ketamine (164.1 per 1,000 and 170.0 per 1,000, respectively). Apnea was more frequent with midazolam (51.4 per 1,000), and hypoxia was less frequent in patients who received ketamine/propofol compared to other combinations. The case of laryngospasm was in a patient who received ketamine, and the aspiration and intubations were in patients who received propofol. When propofol and ketamine are combined, the incidences of agitation, apnea, hypoxia, bradycardia, hypotension, and vomiting were lower compared to each medication separately.

Conclusions: Serious adverse events during procedural sedation like laryngospasm, aspiration, and intubation are exceedingly rare. Quantitative risk estimates are provided to facilitate shared decision-making, risk communication, and informed consent.

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Procedural sedation and analgesia (PSA) is routinely performed in the emergency department (ED) to facilitate potentially painful procedures by alleviating pain, anxiety, and suffering.[1] PSA involves the use of short-acting analgesic and sedative medications to enable clinicians to perform procedures

From the Department of Emergency Medicine (MFB, WIG, JRA, EPH), the Division of Preventive, Occupational, and Aerospace Medicine (MHM, PB), the Mayo Medical Library (PJE), and the Kern Center for the Science of Health Care Delivery (MFB, PB, MHM, EPH), Mayo Clinic, Rochester, MN; and the Department of Emergency Medicine, University of Minnesota Medical School, and the Department of Emergency Medicine, Hennepin County Medical Center (JRM), Minneapolis, MN.

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Supervising Editor: Christopher Carpenter, MD.

Address for correspondence and reprints: M. Fernanda Bellolio, MD, MS; Bellolio.Fernanda@mayo.edu.

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effectively and requires monitoring the patient closely for potential adverse effects.

As emergency physicians (EPs), we are uniquely qualified to provide all levels of sedation. ED-based PSA has been shown to be safe when performed by trained EPs.[2–5] Moreover, we have the skill sets for ventilation, airway management, and resuscitation that are necessary to provide safe patient care should an adverse event occur. Expertise in PSA is included as a core competency in emergency medicine (EM) residency training and pediatric EM fellowships.[1]

The use of various analgesic, sedative, and anesthetic agents has been outlined in several guidelines.[1,6,7] Numerous classes and combinations of drugs are commonly used for PSA in the ED.[2,8–21] The use of short-acting sedative agents such as propofol,[22,23] etomidate,[21,24–27] and ketamine,[28–30] for example, has gained widespread acceptance. The American College of Emergency Physicians (ACEP) has developed a clinical policy regarding PSA.[1] Adverse event reporting for PSA, however, has been heterogeneous.

Given the frequent use of PSA by EPs, as well as the continued development of research and clinical evidence for this practice, we conducted a systematic review and meta-analysis to determine the incidence of adverse events during PSA in the ED, including the frequency of events associated with individual drugs and different drug combinations. We anticipate that the results of the review will provide useful information to providers when performing PSA in a given patient, when engaging in risk communication and shared decision-making, and in the informed consent process.

METHODS

Study Design

This was a systematic review and meta-analysis of studies reporting rates of adverse events for commonly used sedation drugs in the ED. A protocol was written before the beginning of the study. This report adheres to recommendations made in the Preferred Reporting Items for Systematic Reviews (PRISMA) statement.[31]

Eligibility Criteria

Types of Studies. We sought original research studies, including randomized controlled trials (RCTs) and observational studies, in which PSA was performed on adults in the ED. Studies performed on patients under 18 years of age were excluded. We did not exclude any studies based on language. We restricted the inclusion to studies published after 2005 to decrease the variability in medications used, depth of sedation, monitoring during sedation (i.e., capnography), training and expertise of providers with sedation, and definitions of adverse events. Studies reporting moderate and deep sedation as defined per ACEP Clinical Policy were included.[1]

Types of Patients and Procedures. All types of medications used for moderate to deep PSA were included. Procedures included orthopedic joint or fracture reductions, laceration repairs, chest tube insertion, electrical cardioversion, abscess incision and drainage, chest tube thoracostomy, upper endoscopy, lumbar puncture, foreign body removal, hemorrhoidectomy, burn wound care, hernia reduction, stool disimpaction, urinary catheter placement, central line placement, nasopharyngoscopy, pelvic exam, and cervix dilation and curettage.

Types of Interventions. To meet inclusion criteria, the sedation had to be performed in the ED by emergency providers, including EM residents, attending physicians, and/or advance practice providers (nurse practitioners or physician assistants). Drugs given alone or in combination, as intravenous (IV) or intramuscular (IM) injection, were included. Drugs received prior to PSA were not included as interventions (e.g., opioids in a patient with fracture that later required fracture reduction with sedation). Patients who received PSA were monitored according to the guidelines of each individual research protocol.

Study Protocol

Search Strategy. A senior expert librarian designed and conducted a comprehensive search of eight electronic databases, including MEDLINE, EMBASE, EBSCO, CINAHL, CENTRAL, the Cochrane Database of Systematic Reviews, Web of Science, and Scopus from inception to January 23, 2015. The Medline search strategy is included in Data Supplement S1 (available as supporting information in the online version of this paper). To identify trials, we searched Scopus (www.scopus.com/).

Study Selection. In phase I, two investigators (WG, PBM), working independently, screened all the titles and abstracts for eligibility. References that were considered potentially relevant were retrieved in full text and assessed for eligibility by two independent reviewers in phase II. Any disagreements were discussed with the clinical lead authors (EPH, MFB) and resolved by consensus.

Data Extraction. Data were extracted independently and in duplicate using a standardized data form (see Data Supplement S2, available as supporting information in the online version of this paper). Disagreements were resolved by discussion and consensus. Data collected included study design and the incidence of each reported adverse event. Data were compared between the two reviewers, and discrepancies were resolved through discussion. We collected details regarding the medications used, including whether a single drug was used (e.g., propofol) or a combination of drugs (e.g., propofol/ketamine). We recorded the total number of patients experiencing events and the total number of procedures performed.

Risk of Bias Assessment. For RCTs, we assessed the risk of bias using the Cochrane Collaboration bias appraisal tool.[32] We assessed the risk of bias for cohort studies using the Newcastle Ottawa scale.[33] We assessed clinical heterogeneity by determining whether the characteristics of participants, interventions, outcome measures, and timing of outcome measurement were similar across studies.

Missing Data. We collected outcomes as included in the published report and contacted authors by e-mail if data were missing or unclear. If data were still missing after attempting to contact the author, we classified the study as unclear. If data were not reported for a particular outcome, this was also noted in the data extraction form.

Variable Criteria of Outcomes. The included studies defined outcome events such as hypoxia and hypotension using different criteria. Data Supplement S3 (available as supporting information in the online version of this paper) shows the definition used in each study. We analyzed the outcomes based on the study definition. For the outcome of hypoxia, there were studies that defined it as an oxygen saturation of less than 85, 90, 92, 93, 94, and 95%. For the outcome of hypotension, one study defined it as systolic blood pressure (sBP) < 70 mm Hg, others as < 90 mm Hg, and others as < 100 mm Hg. Two studies used mean arterial pressure instead of sBP.

Outcome Measures

In determining which adverse events to extract and report, we followed previous reported outcomes in the PSA literature and collaborated with a content expert on PSA (JRM). After discussion, we reached consensus on the following outcome measures: agitation, apnea, aspiration, bradycardia, bradypnea, hypotension, hypoxia, intubation, laryngospasm, nausea, and vomiting. Subclinical respiratory depression was not analyzed as outcome but was recorded as a marker of more rigorous monitoring. It was defined as loss of end-tidal CO_2 ($ETCO_2$) waveform or change in $ETCO_2$ of more than 10 mm Hg.

Data Analysis

We used OpenMeta[Analyst][34] software for meta-analyses following a random-effects model as described by DerSimonian-Laird. I^2 was used to quantify the degree of statistical heterogeneity between studies. To account for any heterogeneity in clinical and methodologic differences between studies, we used a random-effects model. Random-effects modeling uses a different formula to calculate more conservative 95% confidence intervals (CIs). The effects of treatment are assumed to vary around some overall average treatment effect, as opposed to a fixed-effects model, in which it is assumed that each study has the same fixed common treatment effect. We estimated the incidence per 1,000 patients with 95% CI. When the number of events was zero, we calculated the CI using the modified Wald method.[35] We used Cohen's unweighted kappa to measure chance corrected agreement between reviewers for phase II of the study selection process.

Subgroup Analysis. Because of variation in the cutoff and definition of hypoxia in different studies, we performed a subgroup analysis for the incidence of hypoxia by oxygen saturation (SO_2).

Sensitivity Analysis. We performed the following a priori selected sensitivity analyses, excluding observational studies and reporting results from RCTs, and for studies that reported subclinical depression, we analyzed the results as a separate group.

RESULTS

Description of Included Studies

Figure 1 shows the study selection process. The search strategy identified 2,046 records for review. After screening the titles and abstracts and removing duplicates, we identified 465 potentially relevant studies. After full-text review, 55 articles met inclusion criteria.[8,9,13,17,19,21,27,29,30,36–81] Interobserver agreement (kappa) for phase II of the review was 0.99 (95% CI = 0.98 to 1.0).

Study Characteristics

Data Supplement S4 (available as supporting information in the online version of this paper) describes the 55 included studies. Twenty-five were RCTs and 30 were observational studies (prospective and retrospective cohorts and case series). The studies included 9,652 PSAs conducted in 9,577 patients (<1% underwent more than one PSA).

Quality and Risk of Bias Assessment

The quality of randomized trials is included in Data Supplement S5 (available as supporting information in the online version of this paper), and the quality of cohort studies in Data Supplement S6 (available as supporting information in the online version of this paper). Most studies had low to moderate risk of biases. We did not exclude articles based on the quality assessment.

There was some clinical heterogeneity, as studies had variable sample sizes, and there were different indications for sedation, including orthopedic joint or fracture reductions, laceration repairs, chest tube insertion, abscess incision and drainage, upper endoscopy, and lumbar puncture, among others. However, we thought that it was reasonable to summarize the data, as the procedures were all performed in the ED and required patients to be sedated to tolerate the procedure. All included studies were for moderate and deep sedations. The timing for measurement of the outcomes was similar across studies, as sedation is a resource-intensive and closely monitored procedure.

We found a range from low to high statistical heterogeneity (heterogeneity quantified as I^2 and displayed in Tables 1–3), with low statistical heterogeneity in the outcomes of apnea, aspiration, bradycardia, intubation, and laryngospasm; moderate heterogeneity in the outcomes of agitation, hypotension, and vomiting; and high statistical heterogeneity in the outcome of hypoxia.

Outcomes

A total of 9,652 procedural sedations were included. Table 1 shows the incidence of adverse events per 1,000 sedations. The most frequent events were hypoxia, vomiting, hypotension, and apnea. Hypoxia occurred in 40.2 per 1,000 sedations (95% CI = 32.5 to 47.9); vomiting, 16.4 per 1,000 sedations (95% CI = 9.7 to 23.0); hypotension, 15.2 per 1,000 sedations (95% CI = 10.7 to 19.7); and apnea 12.4 per 1,000 (95% CI = 7.9 to 16.9).

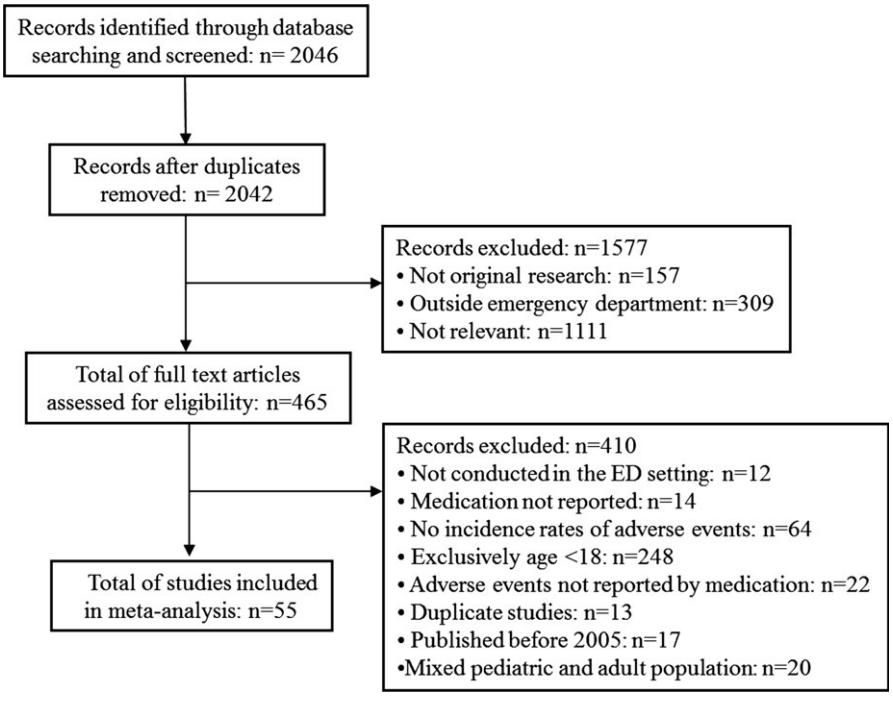

Figure 1. Flow diagram of study selection process.

Table 1
Incidence of Adverse Events per 1,000 Procedural Sedations (Meta-analysis)

Adverse Event	Events per Sedations	Estimate per 1,000	95% CI	I^2 (%)
Agitation	137/6,631	9.8	6.1–13.5	73.6
Apnea	68/3,264	12.4	7.9–16.9	16.05
Aspiration	1/2370	1.2	0.0–2.6	0.0
Bradycardia	11/837	6.5	1.1–11.8	0.0
Hypotension	122/5,801	15.2	10.7–19.7	42.9
Hypoxia	373/7,116	40.2	32.5–47.9	81.8
Intubation	2/3,636	1.6	0.3–2.9	0.0
Laryngospasm	1/883	4.2	0.0–8.5	0.0
Vomiting	100/3,319	16.4	9.7–23	65.3

Severe adverse events requiring emergent medical intervention were rare, with one case of aspiration in 2,370 sedations (1.2 per 1,000), one case of laryngospasm in 883 sedations (4.2 per 1,000), and two intubations in 3,636 sedations (1.6 per 1,000). The incidence of adverse events per medication used is displayed in Table 2.

Results by Outcome

Agitation. A total of 33 studies including 6,631 sedations on 6,558 patients reported the outcome of agitation. The incidence of agitation was 9.8 per 1,000 (95% CI = 6.1 to 13.5). There were 25 of 997 patients who received medication to treat agitation, with an incidence of 27.1 per 1,000 (95% CI = 9.5 to 44.7). Ketamine and ketamine/propofol had the highest rate of agitation. Among the studies that used ketamine, the incidence of agitation was 164.1 per 1,000 sedations (95% CI = 94.8 to 233.5), and among those receiving ketamine/propofol, 48.1 per 1,000 sedations (95% CI = 12.9 to 83.3; see Figure 2).[8,9,13,21,27,30,36–64]

Apnea. Apnea was reported in 22 studies, comprising 68 events in 3,264 sedations on 3,264 patients. The incidence was 12.4 per 1,000 sedations (95% CI = 7.9 to 16.9). The use of midazolam (51.4 per 1,000 sedations, 95% CI = 5.5 to 97.3) and the combination of midazolam/opiate (25.9 per 1,000 sedations, 95% CI = 3.8 to 47.9) had the highest incidence of apnea (see Data Supplement S7a, available as supporting information in the online version of this paper, for forest plots of the incidence of apnea by medication).

Aspiration. A total of 10 studies including 2,370 sedations on 2,370 patients reported the outcome of aspiration. Aspiration occurred in one case (1.2 per 1,000 sedations, 95% CI = 0 to 2.6) receiving propofol and fentanyl. The case of aspiration was a 65-year-old female who underwent sedation with fentanyl and propofol for the reduction of an ankle fracture.[36] The first attempt to reduce the fracture was unsuccessful, and the patient was sedated for a second time 1 hour later. She vomited and aspirated, requiring intubation

Table 2
Meta-analysis of the Events by Medication Used for Sedation

Adverse Events	Etomidate	Ketamine	Ketamine/Propofol	Midazolam	Midazolam/Opiate	Propofol
Agitation						
Events	0/218	97/686	39/912	0/746	0/192	8/3,877
Estimate per 1,000	0	164.1	48.1	0	0	0.7
95% CI	0–20.8	94.8–233.5	12.9–83.3	0–6.2	0–23.6	0–1.6
I^2 (%)	0	90	64	0	0	0
Apnea						
Events		4/381	5/834	15/348	10/277	34/1,424
Estimate per 1,000		10.4	6.1	51.4	25.9	13.2
95% CI		0.3–20.5	0.8–11.4	5.5–97.3	3.8–47.9	6.7–19.7
I^2 (%)		0	0	66	30	15
Aspiration						
Events		0/145	0/24	0/186	0/49	1/1,818
Estimate per 1,000		0	0	0	0	1.0
95% CI		0–31	0–163.1	0–24.4	0–86.8	0–2.4
I^2 (%)		0	NA	NA	0	0
Bradycardia						
Events	9/194	0/114	0/55	0/186	1/31	1/257
Estimate per 1,000	40.2	0	0	0	32.3	7
95% CI	9.7–70.7	0–39.2	0–78	0–24.4	0–94.5	0–17.2
I^2 (%)	17	0	0	NA	NA	0
Hypotension						
Events	4/334	4/232	4/834	7/824	4/323	77/3,254
Estimate per 1,000	10.8	11.8	6.1	6.1	15.4	19.1
95% CI	0–21.8	0–25.6	0.8–11.3	0.8–11.3	2.1–28.8	12–26.3
I^2 (%)	0	0	0	0	0	50
Hypoxia						
Events	24/538	33/660	5/864	32/826	18/392	236/3,688
Estimate per 1,000	35.2	28.3	3.2	51.2	27.5	57.7
95% CI	14.5–56	9.1–47.6	0–7	17.5–84.9	2–53.1	43.6–71.8
I^2 (%)	41	65	0	90	68	85
Intubation						
Events	0/412	0/161	0/55	0/283	0/67	2/2,510
Estimate per 1,000	0	0	0	0	0	1.2
95% CI	0–11.1	0–28	0–78	0–16.1	0–64.9	0–2.6
I^2 (%)	0	0	0	0	0	0
Laryngospasm						
Events		1/563	0/24	0/186		0/110
Estimate per 1,000		4.9	0	0		0
95% CI		0–10.7	0–163.1	0–24.4		0–40.5
I^2 (%)		0	NA	NA		NA
Vomiting						
Events	13/412	71/439	2/889	4/275	2/342	8/814
Estimate per 1,000	21.7	170	1.7	12.1	11.3	7.1
95% CI	6.6–36.9	97.3–242.8	0–4.3	0–25	0.2–22.5	1.4–12.7
I^2 (%)	14	89	0	0	0	0

The I^2 is not calculated when there is only one study in the meta-analysis.

Table 3
Sensitivity Analysis, Events Rates in RCTs

Adverse Event	Events per Sedations	Estimate per 1,000	95% CI	I^2 (%)
Agitation	95/1,397	40.9	25.0–56.1	79.2
Apnea	31/759	21.5	9.5–33.6	29.04
Aspiration	0/348	0.0	0.0–13.2	0.0
Bradycardia	9/598	14.1	0.0–18.1	39.3
Hypotension	30/738	25.0	13.1–36.9	13.1
Hypoxia	194/1,661	87.6	64.3–111.0	82.7
Intubation	0/654	0	0–7.0	0.0
Laryngospasm	0/182	0	0–24.9	0.0
Vomiting	70/669	62.3	34.1–90.4	79.1

RCTs, randomized controlled trials.

for hypoxia. Chest x-ray revealed aspiration pneumonitis. She was admitted to the hospital and extubated 12 hours later with no long-term sequelae. Figure 3 provides the forest plot for the aspiration outcome.[19,36,38,48,49,57,58,61,65,66]

Bradycardia. A total of five studies including 837 sedations on 837 patients reported the outcome of bradycardia. There were 11 events of bradycardia (6.5 per 1,000 sedations, 95% CI = 1.1 to 11.8). The incidence was highest with the use of etomidate (40.2 per 1,000 sedations, 95% CI = 9.7 to 70.7) and midazolam/opiate (32.3 per 1,000 sedations, 95% CI = 0 to 94.5). Figure 4 provides the forest plot for bradycardia.[17,28,40,50,67]

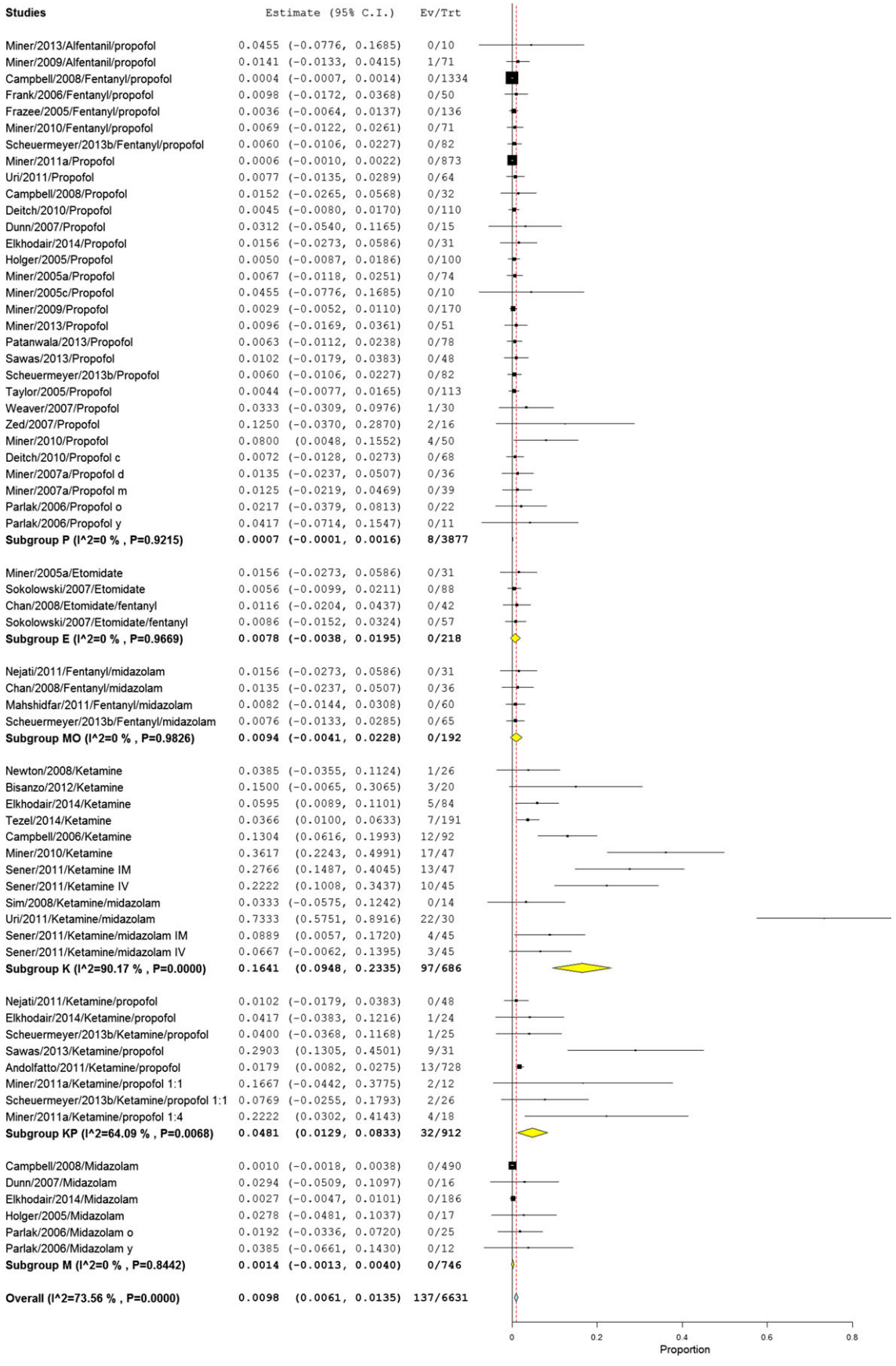

Figure 2. Forest plot of the proportion of patients experiencing agitation, by medication. E = etomidate;[21,42,43] K = ketamine;[30,38,44–50] KP = ketamine/propofol;[8,9,13,38,40,51,52] M = midazolam;[36,38,53–55] MO = midazolam/opiate;[21,40,51,56] P = propofol.[8,13,27,36–39,41,42,48,50,51,53–55,57–64]

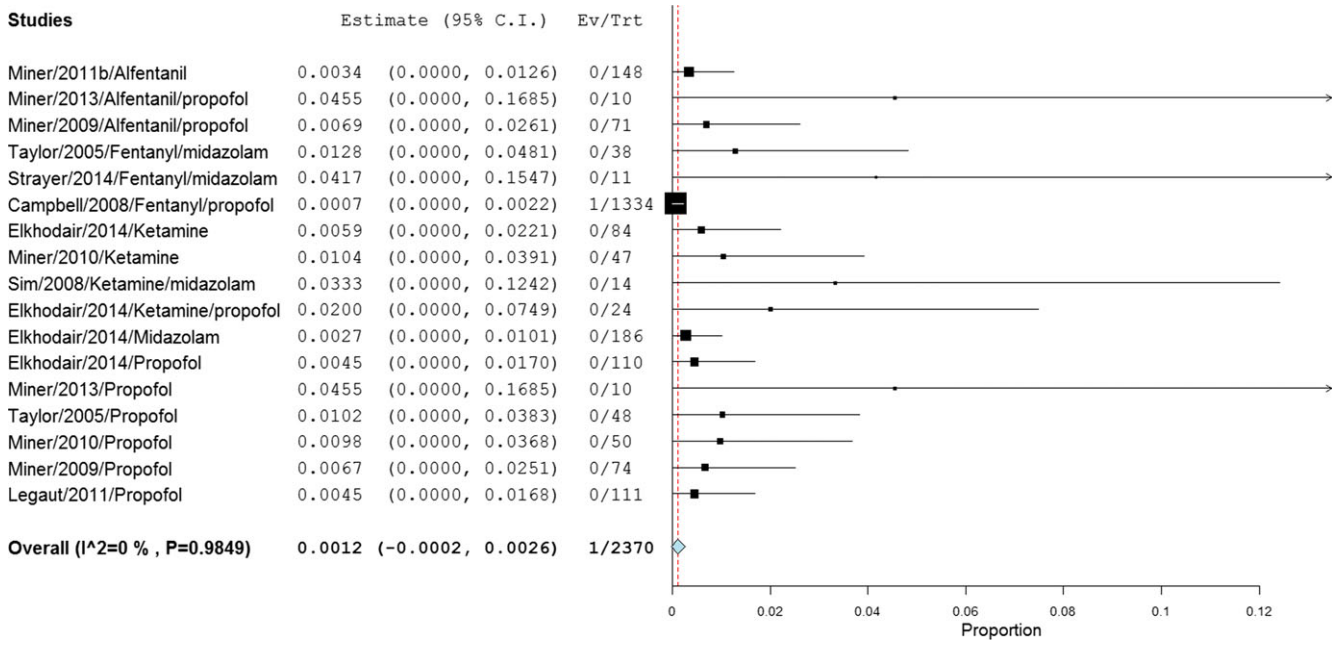

Figure 3. Forest plot of the proportion of patients experiencing aspiration.[19,36,38,48,49,57,58,61,65,66]

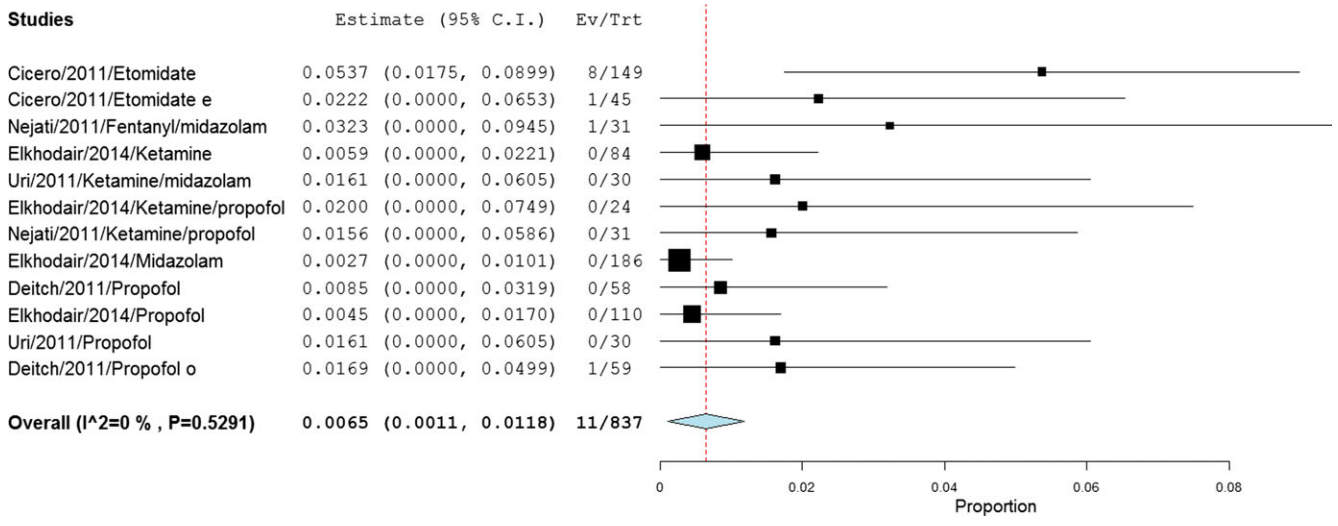

Figure 4. Forest plot of the proportion of patients experiencing bradycardia.[17,38,40,50,67]

Hypotension. A total of 27 studies including 5,801 sedations on 5,801 patients reported the outcome of hypotension. The incidence was 15.2 per 1,000 sedations (95% CI = 10.7 to 19.7).

The incidence was highest with the use of propofol (19.1 per 1,000 sedation, 95% CI = 12 to 26.3) and midazolam/opiate (15.4 per 1,000 sedations, 95% CI = 2.1 to 28.8). Figure 5 shows the forest plot for hypotension.[17,21,24,27,36,38,40,48,50–53,58,59,61,63,67,77]

Hypoxia

Hypoxia was reported in 42 studies, comprising 373 events in 7,116 sedations on 7,043 patients. The incidence was 40.2 per 1,000 sedations (95% CI = 32.5 to 47.9). The incidence was highest with the use of propofol (19.1 per 1,000 sedation, 95% CI = 12 to 26.3) and midazolam/opiate (15.4 per 1,000 sedations, 95% CI = 2.1 to 28.8; see Figure 6 for the forest plot for hypoxia[9,13,17,19,21,27,30,36–40,42–46,48–53,55,57–64,66–71,73,75,76,78,79]).

Intubation

Nineteen studies reported the outcome of intubation on 3,636 sedation and 3,636 patients. There were two intubations (1.6 per 1,000 sedations, 95% CI = 0.3 to 2.9) that occurred in patients that received propofol. One study[37] described an intubation in a 18-year-old male with a history of mild asthma who underwent sedation for distal radius fracture. During the sedation, he developed apnea, hypoxia (nadir SpO_2 of 75%), and emesis. The patient was intubated for 30 minutes. In the 95 minutes before sedation, he received morphine, fentanyl, and lorazepam intravenously. The other case[36] was intubation after aspiration in a patient that underwent sedations for an

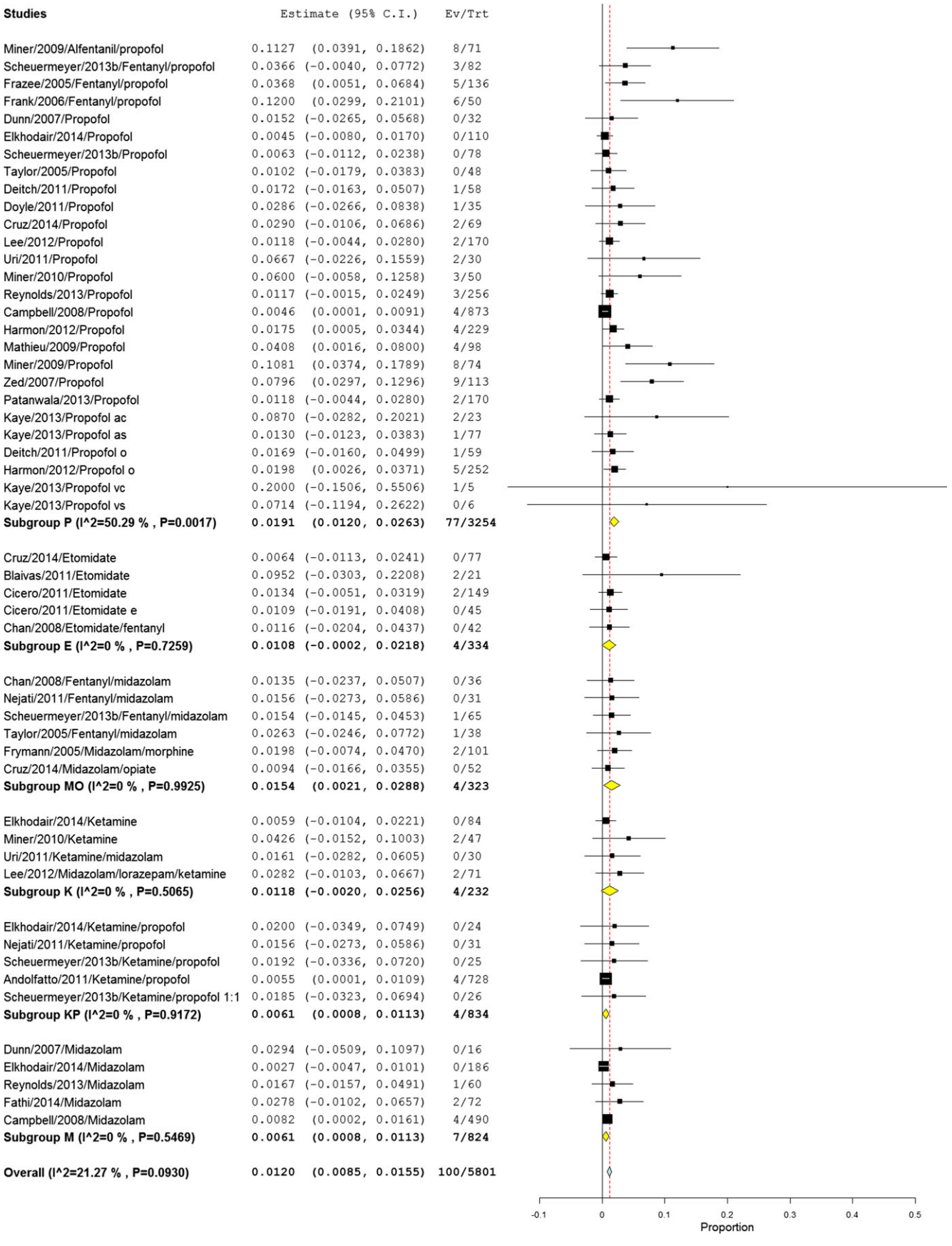

Figure 5. Forest plot of the proportion of patients experiencing hypotension, by medication. E = etomidate;[17,21,68,69] K = ketamine;[38,48,50,70] KP = ketamine/propofol;[38,40,51,52] M = midazolam;[36,38,53,71,72] MO = midazolam/opiate;[21,40,51,61,69,73] P = propofol.[24,27,36,48,50,51,53,58,59,61,63,67,69–71,74–77]

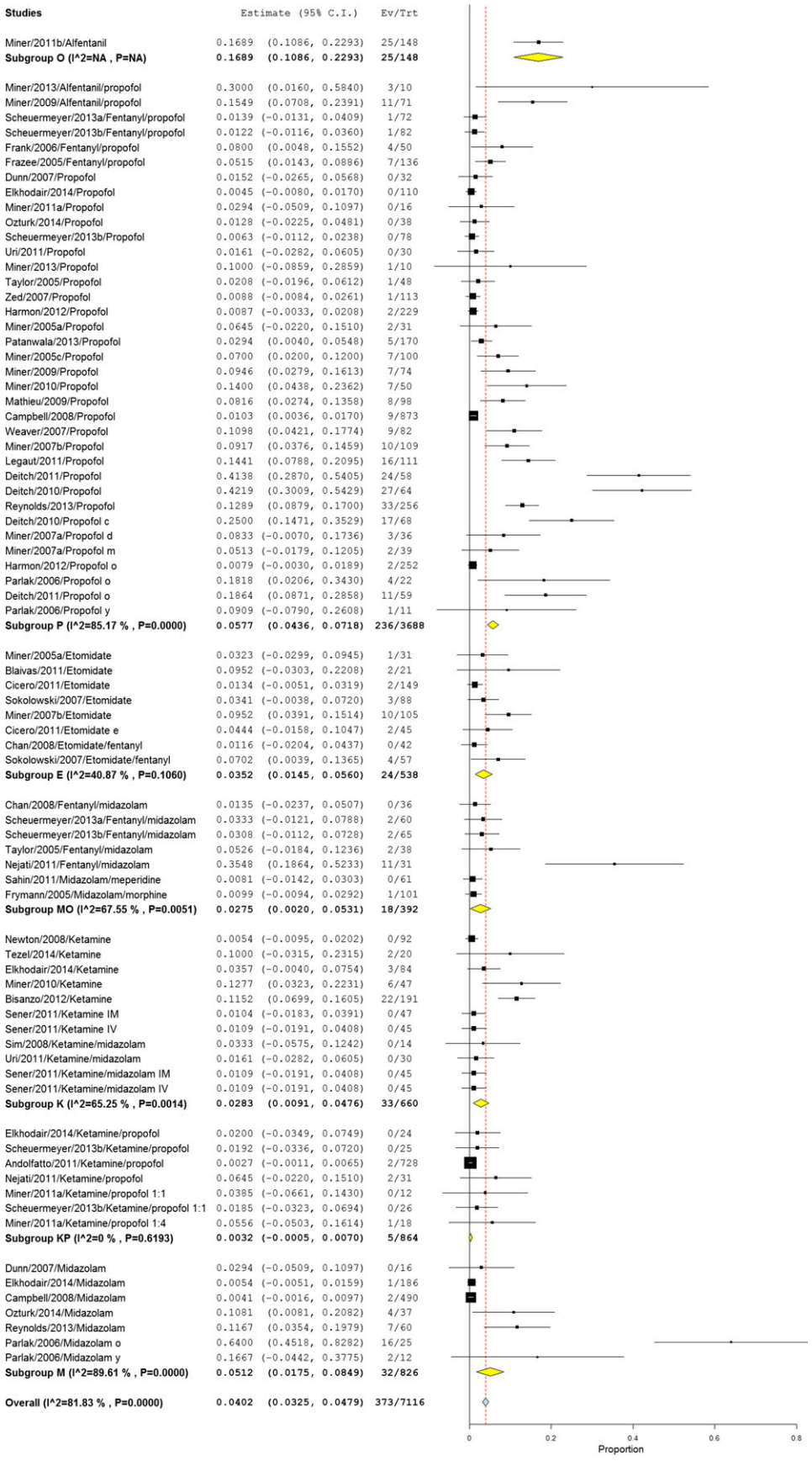

Figure 6. Forest plot of the proportion of patients experiencing hypoxia, by medication. E = etomidate;[17,21,42,43,64,68] K = ketamine;[30,38,44–46,48–50] KP = ketamine/propofol;[9,13,38,40,51,52] M = midazolam;[36,38,53,55,71,78] MO = midazolam/opiate;[21,40,51,52,61,73,79] O = opiate;[19] P = propofol.[13,27,36–39,42,48,50–53,55,57–64,66,67,71,75,76,78]

ankle fracture (see Figure 7 for the forest plot for intubation[17,19,21,36–38,40,42,43,48,50,57–60,62,66,67,71,78]).

Laryngospasm

Five studies including 883 sedations reported the outcome of laryngospasm. Laryngospasm occurred in one patient (4.2 per 1,000 sedations, 95% CI = 0 to 8.5) who received ketamine and who was managed conservatively per authors' report.[38]

Vomiting

A total of 25 studies including 3,319 sedations on 3,319 patients reported vomiting. The incidence was 16.4 per 1,000 sedations (95% CI = 9.7 to 23.0). The use of ketamine (170.0 per 1,000 sedations) had the highest incidence of vomiting (see Data Supplement S7b, available as supporting information in the online version of this paper, for the forest plot of the incidence of vomiting by medication).

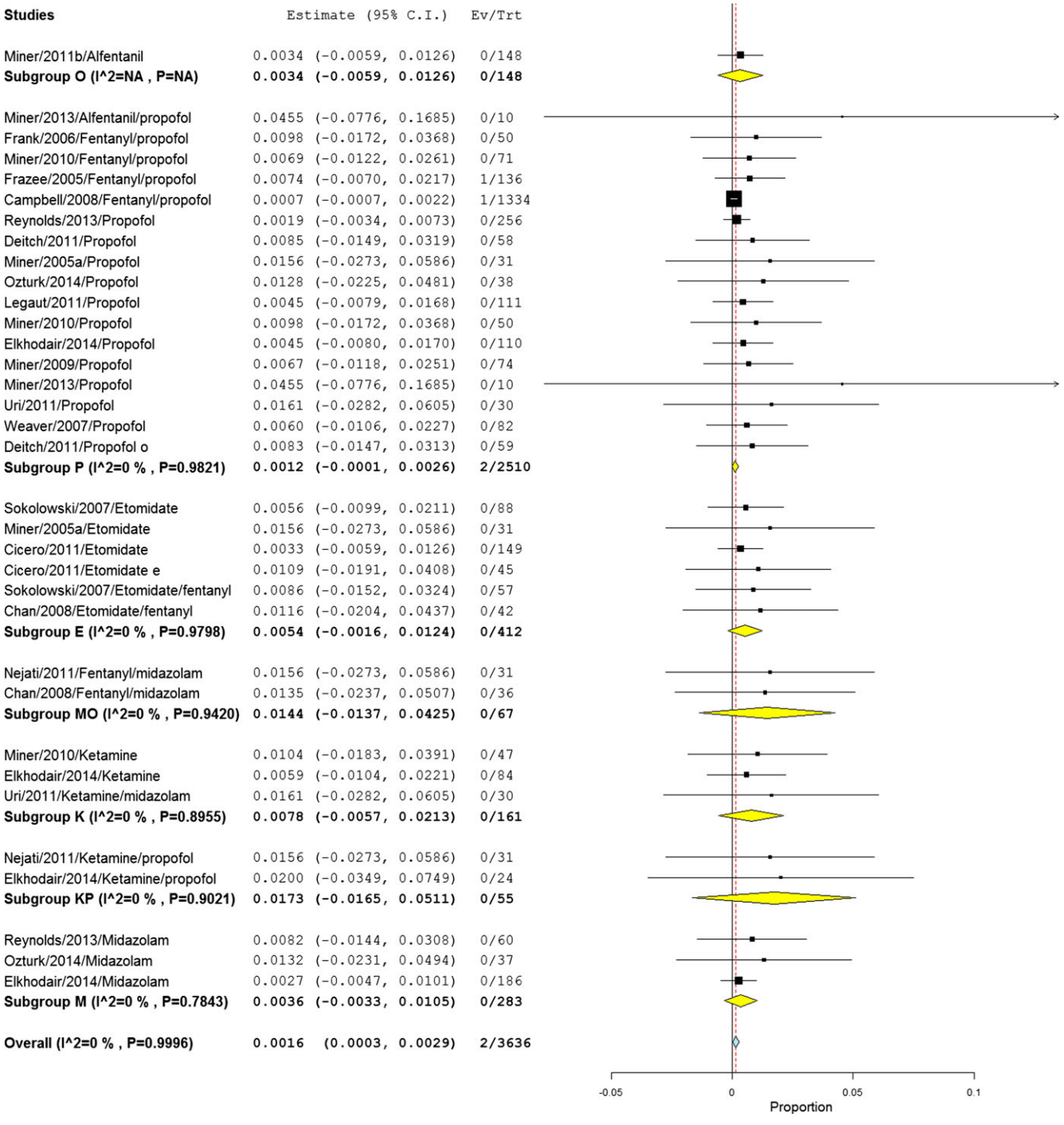

Figure 7. Forest plot of the proportion of patients undergoing intubation, by medication. E = etomidate;[17,21,43,60] K = ketamine;[38,48,50] KP = ketamine/propofol;[38,40] M = midazolam;[38,71,78] MO = midazolam/opiate;[21,40] O = opiate;[19] P = propofol.[36–38,42,48,50,57–59,62,66,67,71,78]

Subgroup Analysis

A subgroup analysis was created based on each study's definition of hypoxia. Studies that had cut off for hypoxia of $SO_2 < 90\%$ had an incidence of hypoxia 23.0 per 1,000 sedations, compared to cutoff of $SO_2 < 94\%$ with an incidence of 73.1 per 1,000 sedations and $SO_2 < 95\%$ with an incidence of 230.7 per 1,000 sedations (see Data Supplement S8, available as supporting information in the online version of this paper, for the forest plot of the subgroup analysis of hypoxia by study definition).

Sensitivity Analyses

After excluding 30 observational studies, a sensitivity analysis of 25 RCTs was performed (see Table 3). When analyzing the incidence of adverse events in PSA in RCTs, we found that the incidence of most of the events was significantly higher, i.e., agitation incidence of 41.1 versus 9.8 per 1,000 in the overall meta-analysis, apnea 21.5 versus 12.4, hypoxia 87.6 versus 40.2, and vomiting 62.3 versus 16.4. This difference in the incidence of events does not appear to be related to the medication used in the RCTs vs observational studies (chi-square test $p = 0.79$).

A sensitivity analysis of 20 studies that reported measures of subclinical respiratory depression was performed. The incidence of bradycardia (20.8 vs. 6.5 per 1,000), hypotension (32.4 vs. 15.2), hypoxia (99.7 vs. 40.2), and intubation (6.1 vs. 1.6) were higher in the sensitivity analysis when compared to the overall meta-analysis (see Table 4).

DISCUSSION

We report the incidence of adverse events that occurred during PSA conducted in the ED. We included 55 different studies comprising nearly 10,000 sedations. The incidence of severe adverse events requiring emergent interventions such as laryngospasm, intubation, or aspiration was low. We did not find any reported deaths in this cohort of sedations in the ED. Severe adverse events requiring emergent medical intervention were infrequent, with one case of aspiration in 2,370 sedations (1.2 per 1,000), one case of laryngospasm in 883 sedations (4.2 per 1,000), and two intubations in 3,636 sedations (1.6 per 1,000). Our results are similar to previous studies, where respiratory events leading to serious adverse outcomes, such as aspiration, unplanned intubation, or cardiac arrest, were exceedingly rare.[82,83]

Table 4
Sensitivity Analysis, Events Rates in Studies That Reported Measures of Subclinical Respiratory Depression*

Adverse Event	Events	Estimate	95% CI	I^2 (%)
Agitation	38/1,410	12.9	4.5–21.4	57.4
Apnea	22/776	19.8	9.6–30.0	6.7
Aspiration	0/410	0.0	0.0–11.2	0.0
Bradycardia	11/373	20.8	6.4–35.1	0.0
Hypotension	75/1,714	32.4	19.4–45.4	61.0
Hypoxia	235/2,415	99.7	76–123.3	87.6
Intubation	1/1,031	6.1	1.4–10.8	0
Laryngospasm	0/191	0.0	0–23.7	NA
Vomiting	12/719	8.7	2–15.4	0

*Subclinical respiratory depression was defined as studies that measured capnography, CO_2 waveform, or end-tidal CO_2 during procedural sedation.

Emergency physicians are uniquely qualified to provide all levels of sedation.[1] Safe and effective sedation and analgesia in the ED is a critical skill that is core to the practice of EM. Before performing PSA, the clinician should discuss the risks, benefits, and alternatives of the procedure and the planned sedation with the patient. Data from this review will help inform the clinician and the patient regarding the incidence of complications and side effects of PSA.

Successful performance requires recognition of not only pitfalls associated with the medications but also consideration for the complexity of patients' underlying physiology and degree of illness or injury. Patients that require PSA in the ED are at increased risk of complications secondary to the emergent nature of the conditions that brought them to the ED and the need for pain and anxiety management to successfully accomplish an intervention or diagnostic procedure. The high-risk nature and comorbidities in these patients may include underlying cardiopulmonary disorders, multiple trauma, head trauma, or intoxication.[1]

Detectable respiratory events such as hypoxia and apnea are common and may be precursors of more serious events during PSA.[11,39,84,85] In an attempt to minimize these adverse events further, the routine use of capnography monitoring during PSA has been recommended,[1] as capnography allows the detection of hypoventilation and apnea earlier than pulse oximetry and/or clinical assessment alone.[39] Similar to the findings of the ACEP policy group, our sensitivity analysis evaluating the incidence of events in studies that measured and reported subclinical respiratory depression showed higher rates of hypoxia in these patients. Moderate to deep sedation can cause respiratory and cardiovascular depression,[1] and it is possible that patients in the studies that measured subclinical respiratory depression had overall better monitoring and more strict reporting and surveillance of findings and might explain the higher incidence of hypoxia, bradycardia, and hypotension in these studies. When analyzing the incidence of adverse events in PSA in RCTs, we found that the incidence of agitation, apnea, bradycardia, hypotension, hypoxia, and vomiting were higher. A higher incidence in RCTs is likely secondary to more rigorous reporting, the prospective nature of the trials, the existence of a protocol, more complete reporting, and less bias than observational studies.

ACEP has established their evidence in adult PSA as a Level A recommendation for the use of propofol, Level B for etomidate and the combination of propofol and ketamine, and Level C for the use of ketamine alone. Brief-acting sedative agents confer shorter periods of impaired levels of consciousness[86–88] and subsequently less risk for adverse respiratory events.[1,2,89–91] An additional benefit to shorter periods of patient impaired consciousness is a reduction of patient monitoring time that allows reduced allocation of intense patient monitoring periods by medical and nursing staff.[1] We found

that there is not a single agent or combination that outperforms compared to the others: agitation was higher with ketamine (27 per 1,000 required medications to treat periprocedural agitation), apnea was higher with midazolam combined with opiates, and bradycardia was higher with etomidate and midazolam combined with opiates. Hypotension occurred with all the medications used for sedation and was higher with propofol and midazolam combined with opiates. Hypoxia was more frequent with propofol and midazolam. The case of laryngospasm was in a patient that received ketamine, and the aspiration and intubations were in patients receiving propofol.

Previous studies suggested benefit when combining propofol with ketamine, including reduction in hypotension and respiratory depression secondary to increases in circulatory norepinephrine induced by ketamine, decrease in vomiting and agitation by the antiemetic and anxiolytic properties of propofol, and reduction in concomitant analgesic needs.[8,9,13,18,40,41,89,92] In our systematic review, when propofol and ketamine were combined, the incidence of agitation, apnea, hypoxia, bradycardia, hypotension, and vomiting were lower compared to each medication separately.

These data provide useful information when allocating resources at the bedside and training providers. The data can also inform providers and assist in communicating the risks of the procedures, in engaging patients in shared decision-making, and in obtaining informed consent for procedural sedation. To help inform the patients at our institution, we have created a pocket card for the providers who will be conducting the procedural sedation; this tool has been received favorably by our patients and physicians. The pocket card (see online Data Supplement S9, available as supporting information in the online version of this paper) and a link to a video that demonstrates how to provide this information to patients is available: https://www.youtube.com/watch?v=dxMldyOgzpc&feature=youtu.be.

In adults presenting to the ED, sedation is safe and effective in providing increased patient comfort and ease of procedural performance. The safest and most effective medication or combination of medications for sedation is yet to be determined. No single drug is ideal for all situations. Consensus for standardizing definitions for reporting adverse events in PSA among adult and pediatric patients needs to be reached and implemented to better compare the optimal agents between studies.[93]

LIMITATIONS

There were limitations in the included studies, as well as in our review. The major limitations are the variation in the definitions for the outcomes that were provided in the studies. There is lack of standardization in the reporting of the outcomes, and this may impact the estimates. Not all studies reported all the outcomes of interest in the meta-analysis. Studies using capnography and other measures of subclinical respiratory depression are likely to detect hypoxia and respiratory events earlier than those that did not reported measures of subclinical respiratory depression. When hypoxia is defined as SO_2 lower than 95%, the incidence is 10 times higher (231 per 1,000 than when we define hypoxia as lower than 90% (23 per 1,000). The higher rates are because of higher sensitivity of the detection of hypoxia with cutoff of 95%. The need for intervention after hypoxia, nausea, and hypotension were not explicitly reported in each study. Subclinical respiratory depression was analyzed in the sensitivity analyses but was not used as an outcome, as the occurrence of subclinical respiratory depression is unlikely to directly impact patient outcomes. We included all types of procedures that required sedation, such as electrical cardioversion for unstable patients, orthopedic fracture, or dislocation reductions, etc., increasing the clinical heterogeneity between studies but also increasing the applicability of the findings to ED practice.

Regarding limitations in the systematic review, there were not enough events in some of the medication categories to determine if the risk of the adverse event was higher with certain medications or medication combinations. When pooling rates from studies with very infrequent events, instead of performing a meta-analysis with weighted mean across studies with the weight derived from the variance, we reported a simple proportion in which the numerator is the sum of events and denominator is the sum of sample sizes to avoid the pooled rate become distorted. To decrease selection bias, we included all eligible studies, particularly those with low number of participants. This likely introduced heterogeneity into the analyses. However, we assessed clinical and statistical heterogeneity and accounted for this in the statistical analyses.

To mitigate some of these limitations, we used sensitivity analyses based on study design (randomized trials) and subclinical respiratory depression and one subgroup analysis based on study definition of hypoxia. We limited the review to studies of adults and excluded those with mixed adult and pediatric populations and only included studies published in the past 10 years. We focused on potentially serious outcomes in patients undergoing moderate and deep sedation.

CONCLUSIONS

Serious adverse events such as intubation, laryngospasm, and aspiration during procedural sedation and analgesia in the ED are exceedingly rare. These data summarize the available literature and provide quantitative risk estimates to facilitate shared decision-making, risk communication, and informed consent.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data S1. Search strategy.

Data S2. Example of data collection form in Excel spreadsheet.

Data S3. Definitions of outcomes per study.

Data S4. Description of the included studies.

Data S5. Cochrane Collaboration's tool for assessment of risk of bias in randomized controlled trials.

Data S6. Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies.

Data S7. Apnea and vomiting by medication.

Data S8. Subgroup analysis of hypoxia by study definition (SO_2%).

Data S9. Pocket card with summary of the information.