Internal and Emergency Medicine (2024) 19:1385–1403
https://doi.org/10.1007/s11739-024-03697-2

EM - REVIEW

Safety of procedural sedation in emergency department settings among the adult population: a systematic review and meta-analysis of randomized controlled trials

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Received: 8 April 2024 / Accepted: 25 June 2024 / Published online: 5 August 2024

Abstract

Procedural sedation and analgesia (PSA) are a common practice in emergency departments (EDs), aiming to alleviate pain, anxiety, and discomfort during various medical procedures. We have undertaken a systematic review and meta-analysis with the aim of assessing the incidence of adverse events associated with PSA, including those related to individual drugs and various drug combinations. The study adhered to PRISMA guidelines for a systematic review and meta-analysis of adverse events in ED sedation. A comprehensive search strategy was employed across ten databases, supplemented by searches on clinicaltrials.gov and manual reviews of reference lists. Data extraction focused on medication administration and adverse events. The study considered four types of adverse events: cardiac, respiratory, gastrointestinal, and neurological. Only randomized controlled trials (RCTs) focusing on PSA administered to adult patients within the ED setting were included. The statistical analysis employed OpenMeta Analyst to conduct a one-arm meta-analysis, with findings presented alongside their corresponding 95% Confidence Intervals. Forest plots were constructed to combine and evaluate results, and sensitivity analyses were performed to identify sources of heterogeneity. From a literature search of 4246 records, 32 RCTs were deemed suitable for this meta-analysis. The analysis included 6377 procedural sedations. The most common adverse event was hypoxia, with an incidence rate of 78.5 per 1000 sedations (95% CI = 77.5–133.5). This was followed by apnea and hypotension, with incidence rates of 31 (95% CI = 19.5–41.8) and 28.1 (95% CI = 17.4–38.9) per 1,000 sedations, respectively. Agitation and vomiting each occurred in 15.6 per 1,000 sedations (95% CI = 8.7–22.6). Severe adverse events were rare, with bradycardia observed in 16.7 per 1,000 sedations, laryngospasm in 2.9 per 1,000 sedations (95% CI = −0.1 to 6), intubation in 10.8 per 1,000 sedations (95% CI = 4–17), and aspiration in 2.7 per 1,000 sedations (95% CI = −0.3 to 5.7). Ketamine is found to be the safest option in terms of respiratory adverse events, with the lowest rates of apnea and hypoxia, making it the least respiratory depressant among the evaluated drugs. Etomidate has the least occurrence of hypotension when used alone. Propofol has the highest incidence of hypotension when used alone and ranks second in hypoxia-related adverse events after midazolam. Using combinations of sedating agents, such as propofol and ketamine, has been found to offer several advantages over single drugs, especially in reducing adverse events like vomiting, intubation difficulty, hypotension, bradycardia, and laryngospasm. The combination significantly reduces the incidence of hypotension compared to using propofol or ketamine individually. Despite the regular use of procedural sedation, it can sometimes lead to serious adverse events. Respiratory issues like apnea and hypoxia, while not common, do occur more often than cardiovascular problems such as hypotension. However, the least frequent respiratory complications, which can also pose a threat to life, include laryngospasm, aspiration, and intubation. These incidents are extremely rare.

Keywords Procedural sedation · Emergency department · Adult population · Adverse events · Sedation protocol · Sedation medications · Patient safety · Sedation outcomes · Sedation complications · Sedation monitoring · Sedation guidelines

Abbreviations

PSA	Procedural sedation and analgesia
ED	Emergency department
ACEP	The American college of emergency physicians
RCTs	Randomised control trials

Extended author information available on the last page of the article

Introduction

Procedural sedation and analgesia (PSA) are a common practice in emergency departments (EDs), aiming to alleviate pain, anxiety, and discomfort during various medical procedures, such as joint dislocation reduction, cardioversion, and imaging studies [1, 2]. Studies have demonstrated the safe implementation of PSA in the ED, aided by the adoption of ultra-short-acting sedatives and analgesics, as well as non-invasive monitoring tools like capnography [3, 4]. However, the availability and utilization of sedative and analgesic agents vary across regions and countries, leading to distinct policy statements and guidelines issued by emergency medicine societies, The Royal College of emergency medicine (RCEM) [3] and American College of Emergency Physicians (ACEP) [4].

PSA are crucial in the ED for effectively managing painful procedures and reducing unnecessary admissions and anesthesia [5]. While emergency physicians (EPs) are trained to perform PSA safely, inadequate documentation in the ED underscores the need for improved training and protocols [5]. Comprehensive training programs are essential to enhance documentation practices, emphasizing thorough documentation covering pre-procedural screening, monitoring, and adverse event management. By equipping EPs with necessary skills and knowledge, training programs can standardize PSA practices and mitigate associated risks [5] PSA remains integral to emergency medicine, offering benefits such as reduced waiting times and hospital admissions [6].

Multiple guidelines have detailed the diverse use of analgesic, sedative, and anesthetic medications for PSA in the ED [3, 4, 7]. Short-acting sedative agents like propofol, etomidate, and ketamine are commonly employed for this purpose [7]. The American College of Emergency Physicians (ACEP) has established clinical policies concerning PSA. However, despite these guidelines, there is variability in the reporting of adverse events associated with PSA [9]. Propofol, appreciated for its rapid onset and brief duration, is frequently combined with fentanyl for pain management, despite its respiratory-depressant effects [8]. Etomidate, preferred for its limited effects on cardiovascular and hemodynamic function even in patients with comorbid diseases, is increasingly used but raises concerns regarding adrenal suppression [8]. Ketamine's, preferred for its least respiratory depressant effects compared, making it a safer option in terms of respiratory compromise [8].

In light of the continued evolution of research and clinical evidence surrounding PSA in the ED, we have undertaken a systematic review and meta-analysis with the aim of assessing the incidence of adverse events associated with it, including those related to individual drugs and various drug combinations. This update to the meta-analysis is prompted by the identification of several new randomized controlled trials (RCTs), and considering that previous meta-analyses [9, 10] included observational studies, our approach now focuses solely on RCTs to minimize bias and provide more robust findings. We anticipate that the outcomes of this updated review will furnish valuable insights for healthcare providers engaged in PSA, aiding in informed decision-making, risk communication, and the consent process for patients undergoing such procedures in the ED.

Materials and methodology

Adherence to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines ensured methodological rigor and transparency throughout the meta-analysis process [11]. We created a comprehensive protocol which involved various aspects of systematic review and meta- analysis procedures before the initiation of this study.

Search strategy

A meticulous electronic search strategy encompassing nine databases, including PubMed, MEDLINE, EMBASE, EBSCO, CINAHL, CENTRAL, the Cochrane Database of Systematic Reviews, Web of Science, and Scopus, was undertaken. This exhaustive search aimed to identify relevant literature spanning from the inception until February, 2024. Utilizing a combination of relevant keywords and controlled vocabulary terms, tailored search strategies were employed to optimize the retrieval of pertinent studies. The search strings used are present in the supplementary material of this research paper (Online supplementary file). Furthermore, a manual review of reference lists from obtained trials, as well as prior meta-analyses and review articles, was performed to identify any additional relevant studies that may have been missed during the electronic search process.

Data extraction

Retrieved articles underwent rigorous screening and evaluation. Utilizing the EndNote Reference Library software, duplicates were identified and removed. Subsequently, two independent reviewers (A.G. and F.A.R.) systematically evaluated the remaining articles for relevance. Titles and abstracts were initially screened, followed by a detailed examination of full articles to ascertain eligibility based on predefined inclusion and exclusion criteria. Any discrepancies between reviewers were resolved through consultation with a third author (A.R.K). Meticulous data extraction

involved recording information on medication administration, adverse events, and procedures conducted in the ED setting.

Information was gathered on the administration of medications, differentiating between single-drug treatments such as propofol, ketamine, etomidate, midazolam, and sodium thiosulfate, and combination therapies like propofol/ketamine, ketamine/midazolam, and Alfentanil/propofol. Combination treatments that incorporated an opioid (for instance, etomidate/fentanyl) were also identified and included in the data compilation. The total count of patients who experienced adverse events and the total quantity of sedation administered were recorded from the studies. Additionally, data of each study was also extracted, this is available in Table 1.

Study endpoints

Four kinds of adverse events were considered as the endpoints for our study these were cardiac, respiratory, gastrointestinal and neurological adverse events.

Criteria for outcome variables

In our meta-analysis, we conducted a thorough examination of the criteria utilized across individual studies to define outcome events such as respiratory adverse events like hypoxia and cardiac adverse events such as hypotension. By systematically documenting the variability in outcome definitions across studies, we aimed to enhance our understanding of the heterogeneity present among the included studies. This meticulous approach allowed us to identify potential sources of variation in reported outcomes and to assess their impact on the overall findings of the meta-analysis. No standardized cut-off values were provided for recording the outcomes of bradycardia, apnea, laryngospasm, vomiting, and agitation. Table 1 delineates the variable outcomes of definitions of hypoxia mentioned by individual RCTS.

Selection criteria

Our systematic review and meta-analysis conducted a single-arm analysis to determine the incidence of various adverse events in patients undergoing PSA in the ED, with several outcomes defined above. Only RCTs were included in our study. Furthermore, inclusion of studies was limited to those published post-2005, with the aim of minimizing variability across factors such as medication protocols, sedation depth, monitoring techniques (e.g., capnography), provider training, and adverse event definitions. Only those studies adhering to the American College of Emergency Physicians (ACEP) Clinical Policy definitions for moderate and deep sedation were included [4]. We excluded studies lacking adequate data or those with study designs susceptible to bias, such as case reports, case series, letters, editorials, reviews, or observational studies. Additionally, studies involving patients under the age of 18 were also excluded.

Data synthesis

The OpenMeta Analyst [18] software was utilized to conduct one-arm meta-analysis, focusing primarily on the untransformed proportion as the main metric, ensuring precision up to four decimal places. Findings were presented alongside their corresponding 95% confidence intervals (CI), utilizing a pooled random effects model (DerSimonian and Laird) [12]. In instances where event counts were zero, confidence intervals were derived using the modified Wald method. Heterogeneity between studies was assessed using the I2 statistic, with an I2 of less than 25% indicating low heterogeneity, 25% to 75% indicating moderate heterogeneity, and greater than 75% indicating high heterogeneity. Sensitivity analysis was explored to account for influential studies and subgroup analyses was explored to account for heterogeneity among the studies.

Results

Search results

The PRISMA flow chart (Fig. 1) in the supplementary material provides a comprehensive overview of the systematic review process. The initial search of databases yielded a total of 4248 records. After removing duplicates (n = 396), the number of unique records for screening was 3852. During the screening phase, 1193 records were excluded for various reasons. The main exclusion criteria included records outside the ED (n = 861), no mention of adverse events (n = 89), and records that were not original research (n = 243). Out of the 2652 records sought for retrieval, 1846 records were assessed for eligibility based on inclusion criteria. The exclusion criteria at this stage included elective procedures (n = 29), records without medication mention (n = 52), mixed adult and child populations (n = 98), observational studies (n = 1464), no adverse events reported (n = 61), irrelevant data (n = 9), and other reasons (n = 126). Finally, a total of 32 studies were included in the review [19–50]. The updated review included 7 new studies that were not part of the previous version (10, 19, 20, 27, 30, 39, and 46.47). This indicates an effort to incorporate recent research findings into the updated review.

Table 1 Characteristics of included studies

Study	Country	Design	Medications used	No. of patients	No. of sedations	Median/ Mean Age, yrs	Male (%)	Procedure/s	Hypoxia cutoff
Afzalimoghaddam [19]	Iran	RCT	Diazepam/Fentanyl (DF)	DF: 42	DF: 42	DF: 30.8	DF: 90.5	Anterior Shoulder dislocation	N/A
			Midazolam/Fentanyl (MF)	MF: 39	MF: 39	MF: 32.5	MF: 9.5		
Bahreini [20]	Iran	RCT	Sodium thiopental / Fentanyl (TH)	TH: 49	TH: 49	TH	TH: 89.80	Fracture or dislocation reductions	N/A
							Mean ± SD	Percutaneous pinning	
							37.00 ± 17.70	Hernia reduction	
								Chest tube insertion	
								Lumbar puncture	
			Ketamine/Propofol (KP)	KP: 47	KP: 47	KP	KP: 85.10		
						Mean ± SD			
						35.97 ± 16.59			
Blavias [21]	USA	RCT	Etomidate	21	21	35.9 (SD ± 15.1)	NA	Shoulder reduction	< 95%
Chan [22]	Hong Kong	RCT	Midazolam/Fentanyl (MF)	MF: 36	39	MF: 57 ± 23	MF: 44.4	Joint reduction	N/A
			Etomidate/ Fentanyl (EF)	EF: 42	EF: 42	EF: 56 ± 21	EF: 42.9		
Deitch [23]	USA	RCT	Propofol with capnography (PC)	PC: 68	PC: 68	PC: 31	PC: 48.5	I&D, fracture and dislocation reduction	< 93%
			Propofol without capnography (P)	P: 64	P: 64	P: 37	P: 57.8		
Deitch [24]	USA	RCT	Propofol with high flow O_2 (PO_2)	PO_2: 59	PO_2: 59	PO_2: 37 (IQR 27–55)	PO_2: 41	I&D, fracture and dislocation reduction	< 93%
			Propofol with compressed air (Pc)	Pc: 58	Pc: 58	Pc: 32 (IQR 21.5–45.5)	Pc: 52		
Dottore [25]	Italy	Controlled Trial	Propofol/Fentanyl	10	10	NA	NA	Joint dislocation reduction	N?A
Fathi [26]	Iran	RCT	Midazolam	72	72	41.1 ± 15.3	52.8	Fracture reduction	N/A
Ferguson [27]	Australia	RCT	Propofol (P)	P: 292	P: 292	P Age: 46	P: 49	Upper limb fracture reduction	< 93%
						Median (IQR): (30–62)		Lower limb fracture reduction	
						Range: 19–86		Abscess incision and drainage	

Table 1 (continued)

Study	Country	Design	Medications used	No. of patients	No. of sedations	Median/ Mean Age, yrs	Male (%)	Procedure/s	Hypoxia cutoff
								Shoulder reduction Other joint reduction Cardioversion	
			Ketofol (Ke)	K: 281	K: 281	K Age: 50 Median (IQR): (31–65) Range: 18–95	K: 49		
Holger [28]	USA	RCT	Fentanyl/Midazolam (FM)	F/M:15	F/M:15	NA	NA	Fracture and dislocation reduction, and abscess I&D	
			Midazolam (M)	M:2	M:2				
			Propofol/Fentanyl (PF)	P/F:12	P/F:12				
			Propofol (P)	P:3	P:3				
Jamal [29]	Malaysia	RCT, convenience sample	Ketamine (K)	K: 18	K: 18	K: 28	K: 94	Fracture and dislocation reduction	N/A
			Midazolam/Fentanyl (MF)	MF: 23	MF: 23	MF: 36	MF: 65		
Lemolel [30]	France	RCT	Ketamine (K)	K: 76	K: 76	Median (IQR): 47 (25–68) Range: 18–94	K: 57	Fracture reduction Dislocation reduction	< 92%
			Ketofol (Ke)	Ke: 76	Ke: 76	Median (IQR): 49 (28–65) Range: 18–94	MF: 49		
Mahshidfar [31]	Iran	RCT	Fentanyl/Midazolam	60	60	28.4 ± 11	88.4	Joint dislocation reduction	N/A
Miner [32]	USA	RCT	Propofol	100	100	39.1	NA	I&D, laceration repair, cardioversion, thoracostomy tube placement, fracture and dislocation reduction, joint aspiration, traction pin placement, nail removal, hernia reduction	< 90%
Miner [33]	USA	RCT	Propofol moderate sedation (Pm)	Pm: 39	Pm: 39	Pm: NA	Pm: NA	Fracture and dislocation reduction	< 90%

Table 1 (continued)

Study	Country	Design	Medications used	No. of patients	No. of sedations	Median/ Mean Age, yrs	Male (%)	Procedure/s	Hypoxia cutoff
			Propofol deep sedation (Ps)	Ps: 36	Ps: 36	Ps: NA	Ps: NA		
Miner [34]	USA	RCT	Etomidate (E)	E: 105	E: 105	E: 36.9 ± 3.1	E: NA	I&D, fracture and dislocation reduction, traction pin placement, cardioversion, chest tube placement, foreign body removal	< 92%
			Propofol (P)	P: 109	P: 109	P: 40.4 ± 14.5	P: NA		
Miner [35]	USA	RCT	Propofol (P)	P: 74	P: 74	P: 39 range 18–87	P: 54.1	I&D, fracture and dislocation reduction, traction pin placement, cardioversion, chest tube placement, wound care	< 92%
			Propofol/Alfentanil (PA)	PA: 71	PA: 71	PA: 38 range 18–80	PA: 49.3		
Miner [36]	USA	RCT	Ketamine (K)	K: 47	K: 47	K: 30	K: 53.2	I&D, fracture and dislocation reduction, cardioversion, chest tube placement, traction pin placement	< 92%
			Propofol (P)	P: 50	P: 50	P: 34.5	P: 48		
Miner [37]	USA	RCT	Ketamine/Propofol (1:1) (KP1:1)	KP1:1: 12	KP1:1: 12	KP1:1: NA	KP1:1: NA	Incision and drainage of abscess Fracture/dislocation reduction Cardioversion Chest tube placement	< 92%
			Ketamine/Propofol (1:4) (KP 1:4)	KP1:4: 18	KP1:4: 18	KP1:4: NA	KP1:4: NA		
			Propofol (P)	P: 16	P: 16	P: NA	P: NA		
Miner [38]	USA	RCT	Propofol (P)	P: 10	P: 10	P: 34 range 18–60	P: NA	Fracture and dislocation reduction	< 92%

Table 1 (continued)

Study	Country	Design	Medications used	No. of patients	No. of sedations	Median/ Mean Age, yrs	Male (%)	Procedure/s	Hypoxia cutoff
			Propofol/Alfentanil (PA)	PA: 10	PA: 10	PA: 36 range 20–58	PA: NA		
Miner [39]	USA	RCT	Alfentanil (A)	A: 52	A: 52	A: Median (IQR, range) 32 (21–62, 18–82)	A: 56	Incision and drainage of abscess Fracture/Dislocation reduction	N/A
			Propofol (P)	P: 56	P: 56	P: Median (IQR, range) 36 (23–56, 18–64)	P: 45		
Nejati [40]	Iran	RCT, convenience sample	Propofol/Ketamine (PK), Midazolam/ Fentanyl (MF)	PK: 31	PK: 31	PK: 25 (IQR 23–37)	PK: 80.6	Reduction of bone fractures and deep lacerations	< 90%
				MF: 31	MF: 31	MF: 25 (IQR 20–32)	MF: 80.6		
Ozturk [41]	Turkey	RCT	Midazolam (M)	M: 37	M: 37	43.5 ± 18.4	M: 67.6	Joint dislocation reduction	< 94%
			Propofol (P)	P: 38	P: 38		P: 68.4		
Parlak [42]	Turkey	RCT	< 65 age Midazolam (M <)	M < : 12	M < : 12	M < : 55.0 ± 9.94	M < : 58.3	Cardioversion	< 95%
			< 65 age Propofol (P <)	P < : 11	P < : 11	P < : 55.27 ± 10.0	P < : 36.3		
			> 65 age Midazolam (M)	M > : 25	M > : 25	M > : 75.04 ± 5.13	M > : 44		
			> 65 age Propofol (P)	P > : 22	P > : 22	P > : 73.18 ± 5.31	P > : 54.6		
Sahin [43]	Turkey	RCT	Midazolam/Meperidine	61	61	42 ± 18.5	67.2	Joint dislocation reduction	N/A
Sawas [44]	USA	RCT	Propofol (P)	P: 51	P: 51	45 ± 18	P: 56	Fracture and dislocation reductions, cardioversion, I&D, foreign body removal, burn wound care and chest tube placement	N/A
			Propofol/Ketamine (PK)	PK: 48	PK: 48		PK: 44		

Table 1 (continued)

Study	Country	Design	Medications used	No. of patients	No. of sedations	Median/ Mean Age, yrs	Male (%)	Procedure/s	Hypoxia cutoff
Sener [45]	Turkey	RCT	Ketamine IV (KIV)	KIV: 45,	KIV: 45,	KIV: 35 (IQR 24–40)	KIV: 70	Fracture and dislocation reduction, burn wound care, I&D, laceration repair, foreign body removal, LP, tube thoracostomy, haemorrhoidectomy	<93%
			Ketamine/Midazolam IV (KMIV)	KMIV: 45,	KMIV: 45,	KMIV: 29 (IQR 25–38)	KMIV: 74		
			Ketamine IM (KIM)	KIM: 47,	KIM: 47,	KIM: 27 (IQR 22–33)	KIM: 66		
			Ketamine/Midazolam IM (KMIM)	KMIM: 45	KMIM: 45	KMIM: 31 (IQR 22.5–37)	KMIM: 72		
Stronati [46]	Italy	RCT	Propofol (P)	P: 34	P: 34	P: 67.9(+—12.6)	P:58.5	Direct Cardioversion	<85%
			Midazolam (M)	M: 35	M: 35	M: 65.1(+-11.4)	M: 71.4		N/A
Salen [47]	USA	Prospective trial	Ketamine	K:46	K:46	Mean: 46.4	26 (57.8)	Joint Reducion	
			Etomidate	E:34	E:34	Mean: 51.6	18 (54.4)		
Taylor [48]	Australia	RCT	Propofol (P)	P: 48	P: 48	P: 40.9	P: 83.3	Joint dislocation reduction	<90%
			Midazolam/Fentanyl (MF)	MF: 38	MF: 38	MF: 45.2	MF: 63.2		
Tezel [49]	Turkey	RCT	Ketamine	20	20	23.5, range 21–85	95	Joint dislocation reduction	N/A
Uri [50]	Israel	RCT	Propofol (P)	P: 30	P: 30	P: 44 ± 13.8	P: 63.3	Fracture and dislocation reduction, extensive lacerations	<90%
			Ketamine/Midazolam (KM)	KM:30	KM:30	KM: 46.7 ± 20.1	KM: 53.3		

I&D incision and drainage, *IDU* intravenous/injection drug users, *IM* intramuscular, *IV* intravenous, *LP* lumbar puncture, *RCT* randomized controlled trial

N/A Not available or Adverse event not reported

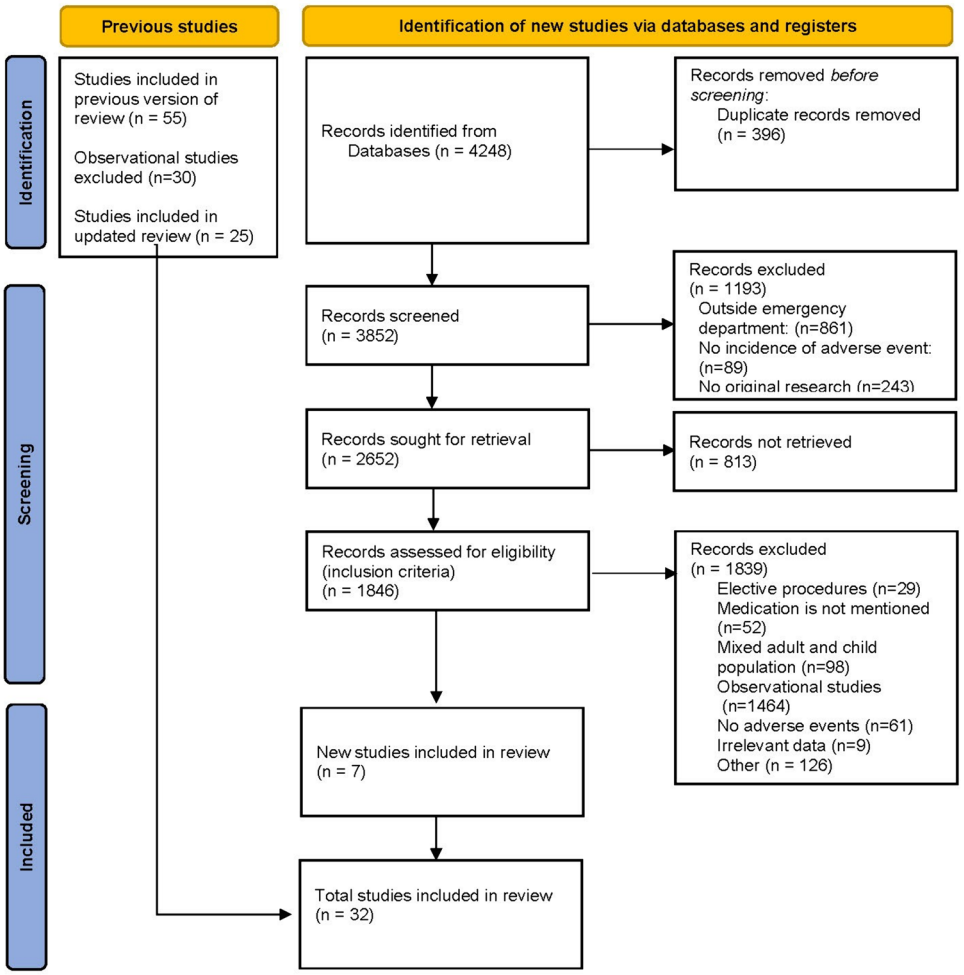

Fig. 1 PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases and registers only

Risk of *bias* of included of included studies

In our meta-analysis, we used the Cochrane Risk of Bias 2 (RoB 2) tool to assess study quality and bias [15]. Two authors (J.K, M.T.K) collaborated on this tool to generate results. In the supplementary material, we provide a detailed assessment of trial quality, with individual risks in Fig. 1a and overall risks as percentages in Fig. 1b, in the supplementary file of this article. Despite some clinical diversity, we did not exclude any study based on risk of bias, this is because most studies had medium to low risk bias.

Baseline characteristics

The study included all medication types for moderate to deep (PSA), administered by emergency medicine providers. Eligibility was for both single and combination drug administrations via IV or IM routes. Sedation was primarily for orthopedic, Incision and drainage, cardiac and followed by a variety of other procedures. Table 1 includes all the data including mean age and gender distributions of the patients included in our analysis. Table 2 highlights the doses and methods of administration of the drugs included in our studies.

Endpoints

A total of 6,377 procedural sedations were analyzed. The most common occurrences were hypoxia, agitation, hypotension, and apnea. Hypoxia was observed in 105.2 per 1,000 sedations (95% CI = 77.5–133.5); agitation, 25.5 per 1,000 sedations (95% CI = 4.9–46); hypotension, 41.7 per 1,000 sedations (95% CI = 20.3–63.2); and apnea 47.6 per 1000 (95% CI = 25.6–69.6). Severe adverse events necessitating immediate medical intervention were infrequent, with only one instance of bradycardia observed in 117 sedations (11.3 per 1000). Summary of meta-analysis of each adverse event is illustrated in Table 3.

Table 2 Doses and methods of administration of the drugs included in our studies

Study	Procedural agent	Dosage	Method of administration
Afzalimoghaddam 2020	Midazolam	0.1 mg/kg	Intravenous (IV)
	Diazepam	0.1 mg/kg	Intravenous (IV)
Bahreini 2020	Ketofol (Combination of Ketamine and Propofol)	0.06 mL/kg	Intravenous (IV)
	Sodium thiopental	0.06 mL/kg	Intravenous (IV)
Blavias 2011	Etomidate	Not mentioned	
Chan 2008	Etomidate	0.1 mg/kg	Intravenous (IV)
	Midazolam	0.05 mg/kg	Intravenous (IV)
Deitch 2009	Propofol	1.0 mg/kg, followed by 0.5 mg/kg as needed	Intravenous (IV)
Deitch 2011	Propofol	1.0 mg/kg, followed by 0.5 mg/kg boluses until adequately sedated	Intravenous (IV)
Dottore 2012	Propofol	1 mg/kg initial dose	Intravenous (IV)
	Etomidate	0.05–0.1 mg/kg initial dose	Intravenous (IV)
Fathi 2014	Midazolam	0.05 mg/kg	Intravenous (IV)
Ferguson 2016	Propofol and Ketofol	Initial bolus of 0.05 mL/kg, additional aliquots of 0.025 mL/kg as needed	Intravenous (IV)
Holger 2005	Propofol	P group: 0.5 mg/kg IV followed by titration to Ramsay Sedation Scale 3 or 4; M group: 1 mg IV every 2 min to Ramsay Sedation Scale 3 or 4	Intravenous (IV)
Jamal 2011	Midazolam	0.05 mg/kg titrated every 3 min up to max dose of 7.5 mg	Intravenous (IV)
	Ketamine	0.5 mg/kg titrated every 3 min up to max dose of 2 mg/kg	Intravenous (IV)
Lemoel 2017	Ketamine	2 doses of 1 mg/kg	Intravenous (IV)
	Ketamine + Propofol	0.5 mg/kg + 0.5 mg/kg	Intravenous (IV)
Mahshidfar 2011	Midazolam	0.1 mg/kg	Intravenous (IV)
Miner 2005	Propofol	Total dose of 1.70 mg/kg	Intravenous (IV)
Miner 2006	Propofol	1.69 mg/kg for Moderate sedation; 1.82 mg/kg for deep sedation	Intravenous (IV)
Miner 2007	Propofol	1 mg/kg bolus followed by 0.5 mg/kg every 3 min as needed	Intravenous (IV)
	Etomidate	0.1 mg/kg followed by 0.05 mg/kg every 3 to 5 min as needed	Intravenous (IV)
Miner 2009	Propofol	1 mg/kg bolus followed by 0.5 mg/kg every 3 min as needed	Intravenous (IV)
	Alfentanil	10 µg/kg IV followed by 1 mg/kg propofol bolus followed by 0.5 mg/kg every 3 min as needed	Intravenous (IV)
Miner 2011	Alfentanil	Total dose of 10 and 15.5 µg/kg	Intravenous (IV)
Miner 2013	Alfentanil	10 µg/kg followed by 1 mg/kg propofol, followed by 0.5 mg/kg every 3 min as needed	Intravenous (IV)
Miner 2017	Alfentanil	10 µg/kg or Propofol 1 mg/kg followed by additional doses of ½ the initial bolus every 3 to 5 min as needed	Intravenous (IV)
	Propofol	1 mg/kg followed by additional doses of ½ the initial bolus every 3 to 5 min as needed	Intravenous (IV)

Table 2 (continued)

Study	Procedural agent	Dosage	Method of administration
Nejati	Propofol/ketamine and Midazolam	A clinical sedation end point was chosen rather than a prescriptive dose (mg/kg) of sedative agent, because it was believed to better reflect common clinical sedation practice, account for variability in patient response, and attempt to standardize all patients to a clinically relevant level of sedation	Intravenous (IV)
OZTURK	Midazolam	0.1 mg/kg initial bolus, additional doses of 0.05 mg/kg in 2 min up to desired sedation level	Intravenous (IV)
	Propofol	1 mg/kg initial bolus, additional doses of 0.5 mg/kg in 3 min if needed	Intravenous (IV)
Parlak	Midazolam	2 mg (1 mL = 1 mg) IV over 20–30 s until RSS-5	Intravenous (IV)
	Propofol	20 mg (1 mL = 10 mg) IV over 20–30 s until RSS-5	Intravenous (IV)
Sahin 2011	Not applicable	NA	NA
Sawas 2011	Propofol	10 mg/cc	Intravenous (IV)
	Ketamine + Propofol	10 mg/cc of ketamine + 10 mg/cc of propofol	Intravenous (IV)
Sener 2011	Ketamine	1.5 mg/kg IV or 4 mg/kg IM, with or without 0.03 mg/kg midazolam	Intravenous (IV) or Intramuscular (IM)
Stronati 2020	Propofol	1 mg/kg initial dose, followed by 0.5 mg/kg every 3 min until satisfactory sedation	Intravenous (IV)
	Midazolam	3 mg initial dose, followed by 2 mg every 2 min until satisfactory response	Intravenous (IV)
Salen 2016	Etomidate or Ketamine	0.1 mg/kg etomidate or 0.5 mg/kg ketamine, additional doses as needed	Intravenous (IV)
Taylor 2005	Not specified	Not specified	Clinician sedation end point
Tezel 2014	Not specified	1 to 2 mg/kg	Intravenous (IV)
URI 2011	Propofol	Titrated slow IV push in 10 mg/10 s boluses, up to 200 mg, followed by repeat dosing as needed	Intravenous (IV)
	Midazolam + Ketamine	0.1 mg/kg midazolam until spontaneous eye closure or up to 5 mg, followed by 1 mg/kg ketamine up to 100 mg to achieve desired sedation level (Ramsay 5 to 6)	Intravenous (IV)

Table 3 Summary of pooled analyses

Adverse events		Events of sedation	Estimate per 1000	95% CI	I^2 (%)
Cardiac	Bradycardia	11/404	16.7	4.4–29	0
	Hypotension	73/1709	28.1	17.4–38.9	48.35
Respiratory	Apnea	86/1769	31	19.5–41.8	48.81
	Aspiration	0/1139	2.7	−0.3 to 5.7	0
	Laryngospasm	0/1210	2.9	−0.1 to 6	0
	Hypoxia	257/3011	78.5	59.8–97.3	80.36
	Intubation	0/864	10.8	4–17	0
Neurological	Agitation	82/2948	15.6	8.7–22.6	65.37
Gastrointestinal	Vomiting	29/390	18.1	9.5–26.8	1.1

Cardiac adverse events

Hypotension

A total of 15 studies including 1709 sedations of which 73 patients reported the adverse effect of Hypotension [14, 20, 21–23, 26, 27, 29, 30, 35, 36, 40, 45, 46, 48, 50]. The incidence of hypotension was 28.1 per 1000 (95% CI = 17.4–38.9). Among the medications examined, sodium thiopental/opiate exhibited the highest estimate of hypotension at 61.2 per 1,000 sedations, with a 95% confidence interval ranging from -5.9 to 128.4. Additionally, propofol was associated with an estimated hypotension rate of 55.7 per 1,000 sedations (95% CI = 26.6–84.7), while etomidate showed a rate of 30.5 per 1000 sedations (95% CI = − 38 to 99). Ketamine had an estimated hypotension rate of 37.3 per 1,000 sedations (95% CI = 7.5–67), and midazolam had a rate of 24.6 per 1,000 sedations (95% CI = − 1.5 to 50.8). The combination of midazolam/opiate showed a rate of 17.2 per 1,000 sedations (95% CI = − 7.4 to 41.8), while diazepam/opiate had the lowest estimate at 11.6 per 1,000 sedations (95% CI = − 20.4 to 43.7). Refer to Table 2 and Fig. 2a for these results, and Table 1c in the supplementary file of our article for additional details for additional details.

Bradycardia

A total of 5 studies including 404 sedations, 11 patients reported the adverse effect of bradycardia [20, 24, 40, 46, and 50]. The incidence of bradycardia was 16.7 per 1000 (95% CI = 4.4 to − 1.6). The data provided presents occurrences of bradycardia associated with various medications used for procedural sedation. Among the medications examined, the estimated rates of bradycardia per 1000 sedations were as follows: propofol 14.6 (95% CI = − 2.7 to 31.8),, ketamine/propofol 12 (95% CI = − 11.9 to 35.9), midazolam 142.9 (95% CI = 26.9–258.8), midazolam/opiate 32.3 (95% CI = − 29.9 to 94.5), and sodium thiopental/opiate 20.4 (95% CI = − 19.2 to 60) Refer to Table 2 and Fig. 3c for these results, and Table 1e in the supplementary file of our article for additional details for additional details.

Respiratory adverse events

Laryngospasm

A total of 7 studies including 1210 sedations of which no patients reported the adverse effect of laryngospasm [27, 32, 33, 35, 36, 44, 47]. The incidence of laryngospasm calculated was 2.9 per 1,000 (95% CI = − 0.1 to − 1.6). Among the medications examined, no instances of

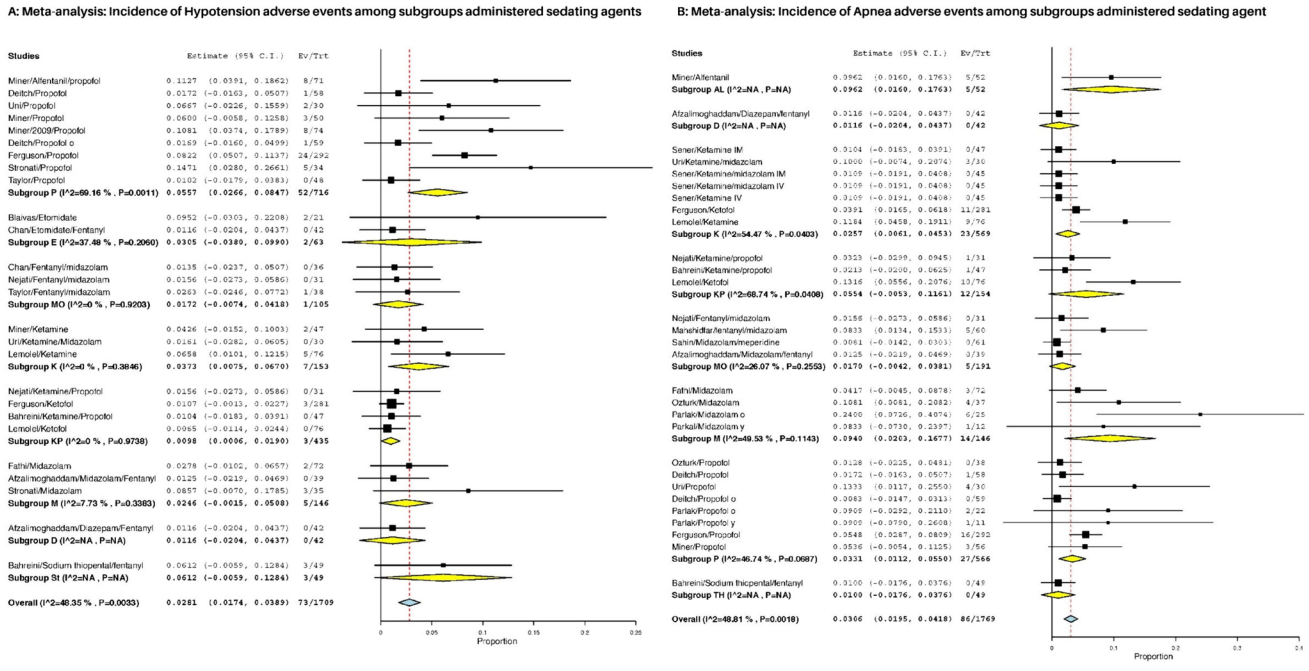

Fig. 2 **a** Meta-analysis: Incidence of hypotension adverse events among subgroups administered sedating agents **b** Meta-analysis: Incidence of Apnea adverse events among subgroups administered sedating agents *P* Propofol *E* Etomidate, *MO* Midazolam and Opiate combination, *K* Ketamine, *KP* Ketamine and Propofol combination, *M* Midazolam, *D* Diazepam, *ST* = Sodium Thiopental, *AL* Alfentanil *Evt/Trt* Events in Relation to Total, Estimate = Estimate per 1000 total events

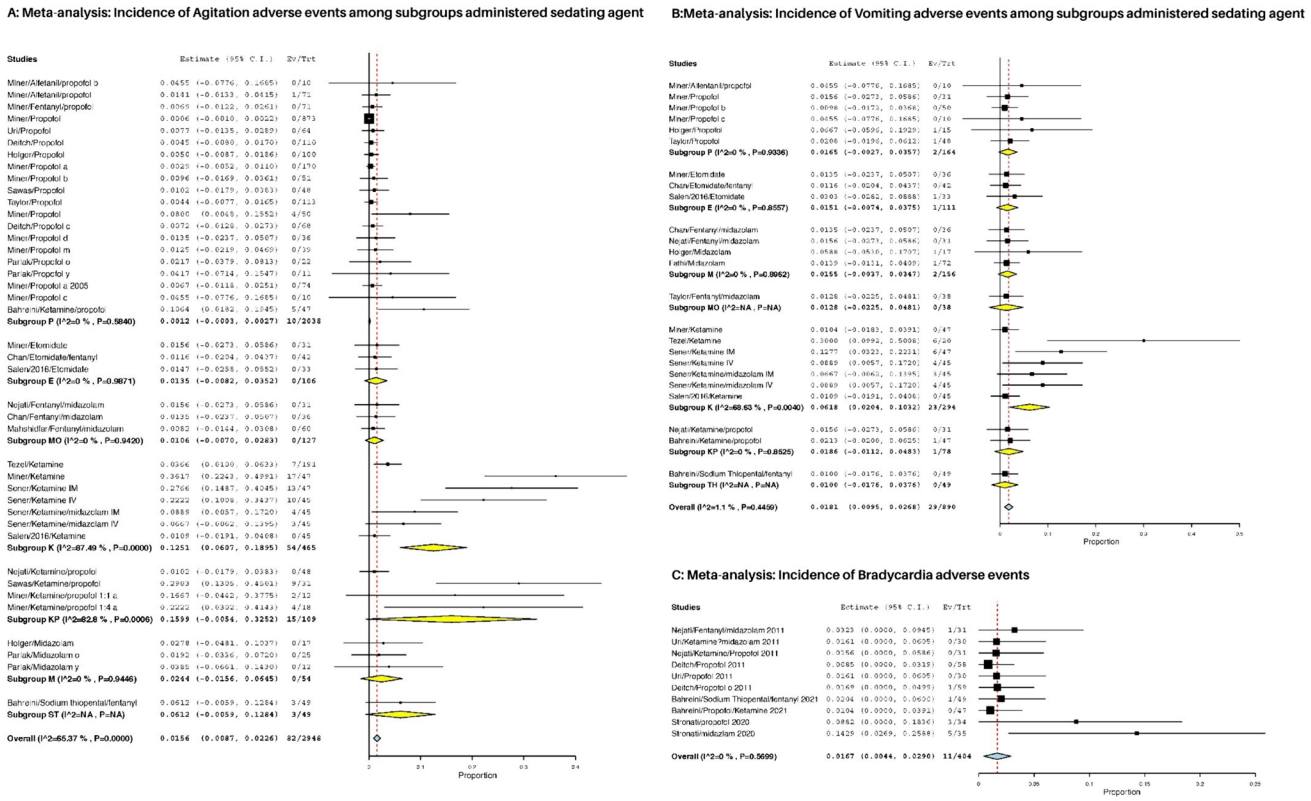

Fig. 3 **a** Meta-analysis: Incidence of Agitation adverse events among subgroups administered sedating agents **b** Meta-analysis: Incidence of Vomiting adverse events among subgroups administered sedating agents **c** Meta-analysis: Incidence of Bradycardia adverse events

P Propofol *E* Etomidate, *MO* Midazolam and Opiate combination, *K* Ketamine, *KP* Ketamine and Propofol combination, *M* Midazolam, *D* Diazepam, *ST* Sodium Thiopental, *AL* Alfentanil *Evt/Trt* Events in Relation to Total, *Estimate* Estimate per 1000 total events

laryngospasm were reported for propofol, ketamine, ketamine/propofol, or alfentanil. However, etomidate showed an estimated laryngospasm rate of 15.6 per 1000 sedations (95% CI = −27.3 to 58.6), while alfentanil had an estimated rate of 9.4 per 1,000 sedations (95% CI = −16.6 to 35.5). Refer to Table 2 and Fig. 4a for these results, and Table 1f in the supplementary file of our article for additional details for additional details.

Apnea

A total of 14 studies including 1769 sedations of which 86 patients reported the adverse effect of apnea [19, 20, 23, 26, 27, 30, 31, 39, 41, 42, 43, 45, 50]. The incidence of apnea was 31 per 1,000 (95% CI = 19.5 to 41.8). Among the medications examined, the estimated rates of apnea per 1,000 sedations were as follows: propofol 33.1 (95% CI = 11.2–55), ketamine 25.7 (95% CI = 6.1–45.3), ketamine/propofol 55.4 (95% CI = −5.3 to 116.1), midazolam 94 (95% CI = 20.3–167.7), midazolam/opiate 17 (95% CI = −4.2 to 38.1), sodium thiopental/opiate 10, and diazepam/opiate 11.6 (95% CI = −20.4 to 43.7). Refer to Table 2 and Fig. 2b for these results, and Table 1i in the supplementary file of our article for additional details for additional details.

Aspiration

A total of 7 studies, encompassing 1139 sedations, investigated the adverse effect of bradycardia during procedural sedation, with no patients experiencing this complication [27, 35–39]. However, our meta-analysis, which offers a broader perspective by aggregating data from various studies, determined that the incidence rate of bradycardia was 16.7 per 1,000 sedations and 95% confidence interval for this rate ranged from 4.4 to −1.6. Propofol exhibited an adverse event rate of 3 per 1,000 sedations, with a 95% confidence interval ranging from −1.3 to 7.2. Ketamine showed an adverse event rate of 10.4 per 1000 sedations, with a 95% confidence interval of −18.3 to 39.1. Ketamine/Propofol had an adverse event rate of 1.8 per 1000 sedations, with a 95% confidence interval of −3.1 to 6.7. Alfentanil exhibited an adverse event rate of 4 per 1000 sedations, with a 95% confidence interval of −4.7 to 12.8. Refer to Table 2 and Fig. 4c

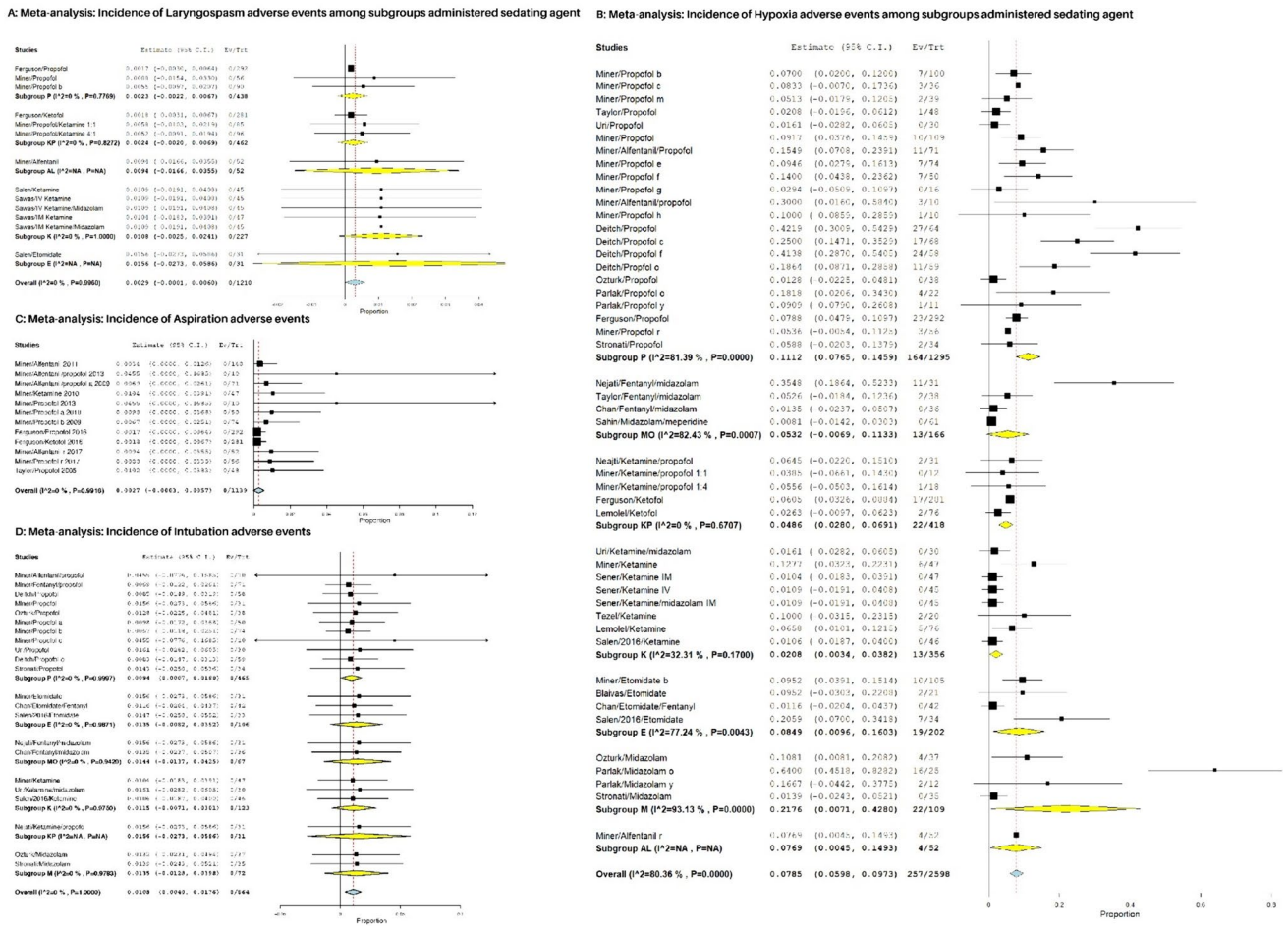

Fig. 4 **a** Meta-analysis: Incidence of Laryngospasm adverse events among subgroups administered sedating agents **b** Meta-analysis: Incidence of Hypoxia adverse events among subgroups administered sedating agents **c** Meta-analysis: Incidence of Agitation adverse events **d** Meta-analysis: Incidence of Intubation adverse events among subgroups administered sedating agents *P* Propofol *E* Etomidate, *MO* Midazolam and Opiate combination, *K* Ketamine, *KP* Ketamine and Propofol combination, *M* Midazolam, *D* Diazepam, *ST* Sodium Thiopental, *AL* Alfentanil *Evt/Trt* Events in Relation to Total, *Estimate* Estimate per 1000 total events

for these results, and Table 1d in the supplementary file of our article for additional details for additional details.

Hypoxia

A total of 23 studies, comprising 2598 sedations, 257 patients experienced the adverse effect of hypoxia during procedural sedation [21–23, 27, 30, 32–43, 45–50]. The reported incidence of hypoxia was 78.5 per 1000 sedations, with a 95% confidence interval ranging from 59.8 to 97.3. Propofol exhibited an adverse event rate of 111.2 per 1000 sedations, with a 95% confidence interval ranging from 76.5 to 145.9. Ketamine showed an adverse event rate of 20.8 per 1000 sedations, with a 95% confidence interval of 3.4–38.2. Ketamine/Propofol had an adverse event rate of 48.6 per 1000 sedations, with a 95% confidence interval of 28.0–69.1. Etomidate exhibited an adverse event rate of 84.9 per 1000 sedations, with a 95% confidence interval of 9.6–160.3. Midazolam demonstrated an adverse event rate of 217.6 per 1000 sedations, with a wide 95% confidence interval of 7.1–428. Midazolam/Opiate had an adverse event rate of 53.2 per 1000 sedations, with a 95% confidence interval of −6.9 to 113.3. Lastly, Alfentanil exhibited an adverse event rate of 76.9 per 1000 sedations, with a 95% confidence interval of 4.5–149.3. Refer to Table 2 and Fig. 4b for these results, and Table 1g in the supplementary file of our article for additional details for additional details.

Intubation

A total of 9 studies, comprising 864 sedations among which no patients experienced the adverse effect of intubation during procedural sedation [22, 23, 35, 36, 38, 41, 46, 47, 50]. The calculate incidence of intubation was 10.8 per 1,000 sedations, with a 95% confidence interval ranging from 4 to 17. The incidence was similar among the

different medications, with ketamine/propofol having the highest incidence of 15.6 per 1000. Refer to Table 2 and Fig. 4d for these results, and Table 1b in the supplementary file of our article for additional details for additional details.

Neurological adverse event

Agitation

A total of 20 studies including 2948 sedations of which 82 patients reported the adverse effect of agitation [20, 22, 23, 28, 31–36, 38, 39, 40, 42, 44, 45, 47–50]. The incidence of agitation was 15.6 per 1000 (95% CI = 8.7 to −22.6). During procedural sedation, the estimated rates of agitation per 1000 sedations varied among the medications examined. Propofol exhibited a rate of 16.5 (with a 95% CI ranging from −2.7 to 35.7), while ketamine showed a significantly higher rate of 61.8 (95% CI = 20.4–103.2). The combination of ketamine and propofol had a rate of 18.6 (95% CI = −11.2–48.3), and etomidate showed a rate of 15.1 (95% CI = −7.4–37.5). Midazolam exhibited a rate of 15.2 (95% CI = −3.7–34.7), midazolam/opiate had a rate of 12.8 (95% CI = −22.5–48.1), and sodium thiopental/opiate had a rate of 10 (95% CI = −17.6 to 37.6). Refer to Table 2 and Fig. 3a for these results, and Table 1h in the supplementary file of our article for additional details.

Gastrointestinal adverse events

Vomiting

A total of 12 studies including 890 sedations among which 29 patients reported the adverse effect of vomiting [20, 22, 26, 28, 33, 36, 38, 40, 45, 47, 48, 49]. The incidence of vomiting was 18.1 per 1000 (95% CI = 9.5 to −26.8). During procedural sedation, the estimated rates of vomiting per 1,000 sedations varied among the medications examined. Specifically, propofol showed a rate of 16.5 (with a 95% CI ranging from −2.7 to 35.7), ketamine exhibited a rate of 61.8 (95% CI = 20.4–103.2), ketamine/propofol had a rate of 18.6 (95% CI = −11.2 to 48.3), etomidate showed a rate of 15.1 (95% CI = −7.4 to 37.5), midazolam presented a rate of 15.2 (95% CI = −3.7 to 34.7), midazolam/opiate had a rate of 12.8 (95% CI = −22.5 to 48.1), and sodium thiopental/opiate and diazepam/opiate had rates of 10 (95% CI = −17.6 to 37.6) and 11.6 (95% CI = −20.4 to 43.7) respectively. Refer to Table 2 and Fig. 3b for these results, and Table 1a in the supplementary file of our article for additional details.

Sensitivity analysis

In a sensitivity analysis of RCTs focusing on procedural sedation, studies mentioning measures of subclinical respiratory depression such as capnography, CO2 waveform, or end-tidal CO2 were examined. The analysis revealed varying adverse event rates per 1,000 sedations across different outcomes. Notably, agitation was reported at a rate of 25.5 (95% CI = 4.9–46), while apnea occurred at a rate of 47.6 (95% CI = 25.6–69.6). Aspiration was not reported in any of the 1091 sedations studied. Bradycardia was observed in 11.3 per 1000 sedations (95% CI = −7.8 to 30.4). Hypoxia had a higher incidence, with a rate of 105.4 per 1000 sedations (95% CI = 77.5–133.3), while intubation was not necessary in any of the 516 sedations. The analysis did not report data on laryngospasm or vomiting. Hypotension was noted in 73 per 1000 sedations (95% CI = 56 to −90). For these results refer to Table 2 in the supplementary file of our article.

Subgroup analysis

Subgroup analysis by procedure

The subgroup analysis by procedure revealed significant differences in outcomes, including apnea, hypotension, hypoxia and as indicated by their respective I2 values. These differences were further explored in subgroups such as orthopedic procedures, multiple procedures, cardiac procedures, and orthopedic plus incision and drainage procedures. Notably, heterogeneity notably decreased when data from only orthopedic and cardiogenic procedures were pooled, suggesting that variability in outcomes could be attributed to the diversity of procedures across studies. Factors like variations in sedation protocols, patient demographics, and monitoring practices may contribute to additional heterogeneity in the results. Refer to Fig. 2a–d which represent Meta-Analysis of Subgroup Analysis undergoing procedures, in the supplementary file of our article.

Discussion

Our meta-analysis meticulously gathers, contrasts, and assesses data from 31 RCTs involving adult patients undergoing procedural sedation in the ED. We've categorized the events into four distinct groups: respiratory (encompassing apnea, laryngospasm, hypoxia, and intubation), cardiac (including bradycardia and hypotension), neurological (agitation), and gastrointestinal (vomiting). Our meta-analysis results show various adverse events due to sedation categorized under cardiac, respiratory, neurological, and gastrointestinal issues. In the cardiac category, bradycardia occurred

at an incidence of 16.7 per 1000 (95% CI = 4.4–29), and hypotension at 28.1 per 1000 (95% CI = 17.4–38.9). For respiratory adverse events, apnea was noted at an incidence of 31 per 1000 (95% CI = 19.5–41.8), while hypoxia was the most prevalent at 78.5 per 1000 (95% CI = 59.8–97.3). Neurological agitation occurred at a rate of 15.6 per 1000 (95% CI = 8.7–22.6). Gastrointestinal vomiting was noted at an incidence rate of 18.1 per 1000 (95% CI = 9.5–26.8). Based on our meta-analysis results and several other studies [8, 12,] each drug exhibits distinct benefits over others in terms of adverse event profiles during procedural sedation but no drug outperforms the other. Ketamine emerges as the safest option overall regarding respiratory adverse events, showcasing the lowest incidence rates of apnea (25.7 events per 1000) and hypoxia (20.8 events per 1000), thus positioning it as the least respiratory depressant among the drugs evaluated. Etomidate stands out for its minimal occurrence of hypotension (30.5 events per 1000) when used as a single drug. However, the combination of ketamine and propofol proves to be the most cardiovascular safe, demonstrating the lowest rates of adverse events in hypotension (9.8 events per 1000) and bradycardia (12 per 1000). Previous research has highlighted Propofol's rapid onset and reduced postoperative recovery time, rendering it a suitable choice for procedural sedation [13, 14]. However, when administered alone, Propofol exhibits the highest incidence of adverse events in hypotension, and it ranks second, following midazolam, in terms of hypoxia-related adverse events.

Utilizing combinations of sedating agents, such as propofol and ketamine, offers several advantages over using single drugs alone, particularly concerning adverse events such as vomiting, intubation difficulty, hypotension, bradycardia, and laryngospasm. The combination exhibits a notably reduced incidence of hypotension (9.8 per 1,000) compared to using propofol or ketamine individually (55.7 and 37.3 per 1,000, respectively). Even though our study indicated a significant risk of intubation in patients receiving the above combination of drugs, it is important to highlight that this combination is safe and efficacious when used correctly. ACEP clinical policy, previous meta-analysis [9, 10] and several previous studies [16, 17, 27, and 30] arrived at a comparable conclusion regarding the safety of combination therapy. Similarly, although to a lesser extent, the combination of midazolam and opiate demonstrates a lower occurrence of adverse events compared to administering midazolam alone, suggesting it may be a safer option for procedural sedation. Our findings strongly suggest that drug combinations offer greater safety advantages over using single drugs in procedural sedation scenarios.

The literature review and meta-analysis reveal a lack of high-quality RCTs on the use of sodium thiopental and alfentanil for procedural sedation in EDs. This data gap hinders the accurate assessment of adverse events. Given this, healthcare providers should cautiously use these sedatives and consider alternatives like ketamine or midazolam, which have more robust safety and efficacy data, until further research is available. Furthermore, a combination of dexmedetomidine and ketamine has also been tried for procedural sedation in the ED. A prospective study by Gregoire et al. [50] demonstrated adequate comfort and pain relief in patients; however, it was associated with longer sedation and recovery times compared to conventional drug regimens. Our study did not evaluate this combination due to the lack of sufficient RCTs, warranting further large-scale trials.

ACEP guidelines and several other studies and previous meta-analyses [9, 10] give the benefit measure of subclinical respiratory depression such as capnography, CO2 waveform or end tidal CO2 during procedural sedation. In our sensitivity analyses, which included studies using these same measures, we found an increased incidence of apnea and hypoxia. This increase could be attributed to the heightened sensitivity of these measures in detecting respiratory adverse events. As a result, studies using these measures reported a higher incidence of these adverse events. This does not necessarily mean that there were more adverse events, but rather that these events were more likely to be detected due to the sensitive nature of the measures used.

The meta-analysis yields crucial insights into the adverse event profiles of various sedating agents, empowering emergency healthcare providers to make informed decisions in agent selection. For instance, prioritizing patient safety, physicians may prefer ketamine over propofol to mitigate hypotension risks. Tailoring sedation to individual patient conditions, such as respiratory complications, allows for personalized care, with ketamine often favored for its lower respiratory depression risks. Additionally, understanding the incidence of adverse events enables proactive risk assessment and vigilant monitoring during procedural sedation. This approach facilitates early detection and intervention, optimizing patient outcomes through dose adjustments, intensified monitoring, or alternative agent considerations.

Limitations and future prospects

First, our meta-analysis faced challenges due to varying outcome definitions in included studies, potentially skewing estimates despite efforts to minimize variability. Standardized outcome definitions could enhance comparability in future research. Furthermore, some studies did not report all outcomes, limiting the scope of our analysis.

Second, research methods that utilize capnography and additional indicators of subclinical respiratory depression are expected to detect hypoxia and respiratory incidents earlier than studies without such measures, introducing heterogeneity between studies. Furthermore, certain medication

categories had limited events, making it difficult to ascertain if the risk of adverse events fluctuated with specific medications or combinations. These may limit the generalizability of our results. Lastly, in an attempt to reduce selection bias, we included all eligible studies in our analysis, even those with a small number of participants. While this approach likely introduced heterogeneity into our analyses, we systematically evaluated both clinical and statistical heterogeneity and addressed these factors in our statistical analyses. Moving forward, future research endeavors should strive to address these limitations by adopting standardized outcome definitions, improving reporting standards, and implementing predefined cut-off values where applicable. Additionally, efforts to minimize clinical heterogeneity through more targeted study inclusion criteria and larger sample sizes may enhance the robustness and generalizability of findings in subsequent meta-analyses.

Conclusions

In the ED, PSA are commonly used to ease the pain and anxiety associated with potentially painful procedures. However, serious adverse events can occur during procedural sedation, despite its routine use.

While respiratory complications like apnea and hypoxia aren't common, they do happen more often than cardiovascular issues such as hypotension, neurological problems like agitation, and gastrointestinal issues like vomiting. However, the least common respiratory events, which can also be life-threatening, are laryngospasm, aspiration, and intubation. These occurrences are extremely rare.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11739-024-03697-2.

Funding None.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Not applicable.

Informed Consent Not applicable.

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