

Adverse Events Rate in Adults Having Procedural Sedation in the Emergency Department: A Systematic Review and Meta-analysis

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Abstract

Background: The use of numerous analgesics, sedative, and anesthetic agents has been outlined in numerous guidelines. Several classes and combinations of medication are commonly used for procedural sedation in the emergency department (ED). **Aim:** This work aims to determine the rate of adverse events for adult patients having procedural sedation in the emergency department. **Materials and Methods:** A systematic search was performed over different medical databases to identify Emergency Medicine studies, which studied the incidence of adverse events in adult patients having emergency procedural sedation. Using the meta-analysis process, either with fixed or random-effects models, we conducted a meta-analysis on overall complications rate as a primary outcome, and incidence of (agitation, aspiration, bradycardia, hypotension, hypoxia, and the need for intubation), as secondary outcomes. **Results:** Twenty-four studies were identified involving 2348 patients. The meta-analysis process revealed that the estimated pooled prevalence of adverse events among adult patients having emergency procedural sedation was (6.61%). The estimated pooled prevalence of each adverse event were (1.92%), (0.18%), (0.97%), (1.71%), (3%), and (2.18%), respectively. **Conclusion:** To conclude, procedural sedation and analgesia (PSA) are routinely performed in the emergency department (ED) to facilitate potentially painful procedures by alleviating pain, anxiety, and suffering serious adverse events during procedural sedation laryngospasm, aspiration, and intubation are exceedingly rare.

Keywords: Adverse events; Adult; Procedural Sedation: Emergency department

Introduction

Many humans presenting to emergency departments (ED) are in an anxious state due to the fact they're in distressing pain (e.g. because of a joint dislocation). Their anxiety is further heightened using some of the painful procedures required for the control of the underlying clinical condition (e.g. reduction of a dislocated joint). Procedural sedation (PS) can be required for sedation, hypnosis, and relaxation for painful methods. It may also be required to provide adequate operating conditions by way of minimizing movement or through inducing amnesia for unpleasant procedures (e.g. wound closure through suturing). When analgesia can't be guaranteed in adults, PS may also be required.^[1]

Emergency physicians frequently encounter agitated patients within the emergency department (ED). Causes of ED-based agitation are numerous, ranging from psychosis to intoxication. Although verbal de-escalation is recommended as first-line

treatment, in some cases this can be ineffective, and medicinal drug administration may be required to save you these patients from harming themselves or others. However, many of those medicines have a relatively slow onset, require empiric dosing, and often require additional medication for calming.^[2]

The use of numerous analgesics, sedative, and anesthetic agents has been outlined in numerous guidelines. Several classes and combinations of medication are commonly used for PSA in the ED. The use of short-acting sedative agents such as propofol, etomidate, and ketamine, for example, has gained widespread acceptance. The American College of Emergency Physicians

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(ACEP) has advanced a clinical policy regarding PSA. adverse event reporting for PSA, however, has been heterogeneous.^[3]

Propofol is a popular emergency department (ED) procedural sedation agent that provides sedation, amnesia, and antiemetic effects; but it may additionally produce respiration depression and hypotension. The dissociative agent ketamine maintains cardiopulmonary stability, however, it can result in extended recovery, emesis, hypersalivation, and hallucinations. The popular combination of propofol and ketamine (“ketofol”) is purported to decrease breathing despair, emesis, and recovery time with the aid of counteracting the poor results of 1 drug with the positive effects of the other, even though the best evidence thus far does not indicate a reduction in the airway and respiratory adverse events relative to propofol alone.^[4]

This work aims to determine the rate of adverse events for adult patients having procedural sedation in the emergency department.

Literature Review

Our review came following the (PRISMA) statement guidelines.^[5]

Study eligibility

The included studies should be in English, a journal published article, and a human study describing adult patients having emergency procedural sedation. The excluded studies were non-English or animal studies or describing pediatric patients.

Study identification

Basic searching was done over the PubMed, Cochrane library, and Google scholar using the following keywords: Adverse events, Adult, Procedural Sedation, Emergency department.

Data extraction and synthesis

RCTs, clinical trials, and cohort studies, which studied the incidence of adverse events in adult patients having emergency procedural sedation, will be reviewed. Outcome measures included overall complications rate as a primary outcome, and on the incidence of (agitation, aspiration, bradycardia, hypotension, hypoxia, and the need for intubation), as secondary outcomes.

Study selection

We found 470 records, 390 excluded based on title and abstract review; 80 articles are searched for eligibility by full-text review; 29 articles cannot be accessed; 16 studies were reviews and case reports; 11 were pediatric studies leaving 24 studies that met all inclusion criteria.

Statistical methodology

The pooling of data, Proportions (%), odds ratios (ORs), with 95% confidence intervals (CI) were done, using MedCalc ver. 18.11.3 (MedCalc, Belgium). According to heterogeneity across trials using the I_2 -statistics; a fixed-effects model or random-effects model were used in the meta-analysis process.

Results

The included studies published between 2005 and 2020. Regarding the type of medication used for sedation, we chose 6 studies using each medication (Propofol, Etomidate, Midazolam, and Ketamine) with 24 total studies included [Table 1].

Regarding patients’ characteristics, the total number of patients in all the included studies was 2348 patients [Table 1].^[6-23]

Table 1: Patients and study characteristics.

N	Author	Year of publication	Medication used for Sedation	Total number of patients
1	Taylor et al. ^[6]	2005	Propofol	48
2	Miner et al. ^[7]	2005	Etomidate	31
3	Sokolowski et al. ^[8]	2007	Etomidate	88
4	Campbell et al. ^[9]	2008	Propofol	873
5	Chan et al. ^[10]	2008	Etomidate	42
6	Chan et al. ^[10]	2008	Midazolam	36
7	Newton et al. ^[11]	2008	Ketamine	26
8	Nejati et al. ^[12]	2011	Midazolam	31
9	Mahshidfar et al. ^[13]	2011	Midazolam	60
10	Nejati et al. ^[12]	2011	Ketamine	48
11	Scheuermeyer et al. ^[14]	2013	Propofol	82
12	dela Cruz et al. ^[15]	2014	Etomidate	77
13	Tezel et al. ^[16]	2014	Ketamine	191
14	Elkhodair et al. ^[17]	2015	Propofol	110
15	Elkhodair et al. ^[17]	2015	Midazolam	186
16	Elkhodair et al. ^[17]	2015	Ketamine	84
17	Kasmaee et al. ^[18]	2019	Propofol	32
18	Das et al. ^[19]	2019	Etomidate	50
19	Carver et al. ^[20]	2019	Ketamine	45
20	Kim et al. ^[21]	2020	Propofol	34
21	Kim et al. ^[21]	2020	Etomidate	36
22	Wang. ^[22]	2020	Midazolam	20
23	Kim et al. ^[21]	2020	Midazolam	35
24	Eberl et al. ^[23]	2020	Ketamine	83

A meta-analysis study was done on 24 studies that described the incidence of adverse events in adult patients having emergency procedural sedation; with an overall number of patients (N=2348) [Table 2].^[6-23]

Each outcome was measured by:

Pooled Proportions (%) for:

- Overall complications rate
- Incidence of agitation
- Incidence of aspiration
- Incidence of bradycardia
- Incidence of hypotension
- Incidence of hypoxia
- Incidence of intubation

Concerning the primary outcome measure,

We found 24 studies reported adverse events with a total number of patients (N=2348).

I₂ (inconsistency) was 90% with a highly significant Q test for heterogeneity (p<0.0001), so the random-effects model was chosen to assess the pooled prevalence.

Using the random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of adverse events among adult patients having emergency procedural sedation was (6.61%) (95% CI=3.558 to 10.534) [Figure 1].

Concerning the secondary outcome measures, I₂ (inconsistency) was 83.6% with a highly significant Q test for heterogeneity (p<0.0001), so the random-effects model was chosen to assess the pooled prevalence.

Using the random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of agitation among adult patients having emergency procedural sedation was (1.92%) (95% CI=0.593 to 3.983) [Figure 2].

I₂ (inconsistency) was 0% with a non-significant Q test for heterogeneity (p>0.05), so the fixed-effects model was chosen to assess the pooled prevalence.

Using the fixed-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of aspiration among adult patients having emergency procedural sedation was (0.18%) (95% CI=0.0247 to 0.489) [Figure 3].

I₂ (inconsistency) was 36.2% with a non-significant Q test for heterogeneity (p>0.05), so the fixed-effects model was chosen to assess the pooled prevalence.

Using the fixed-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of bradycardia among adult patients having emergency procedural sedation was (0.97%) (95% CI=0.255 to 2.142) [Figure 4].

I₂ (inconsistency) was 70% with a highly significant Q test for heterogeneity (p<0.0001), so the random-effects model was chosen to assess the pooled prevalence.

Using the random-effects model, the meta-analysis process

Table 2: Summary of outcome measures in all studies.

N	Author	Primary outcome			Secondary outcomes			
		Overall adverse events Events	Agitation Events	Aspiration Events	Bradycardia Events	Hypotension Events	Hypoxia Events	Intubation Events
1	Taylor et al. [6]	1	0	0	---	0	1	---
2	Miner et al. [7]	1	0	---	---	---	1	0
3	Sokolowski et al. [8]	3	0	---	---	---	3	0
4	Campbell et al. [9]	15	0	1	---	4	9	1
5	Chan et al. [10]	0	0	---	---	0	0	0
6	Chan et al. [10]	0	0	---	---	0	0	0
7	Newton et al. [11]	1	1	---	---	---	0	---
8	Nejati et al. [12]	12	0	---	1	0	11	0
9	Mahshidfar et al. [13]	0	0	---	---	---	---	---
10	Nejati et al. [12]	2	0	---	0	0	2	0
11	Scheuermeyer et al. [14]	4	0	---	---	3	1	---
12	dela Cruz et al. [15]	0	---	---	---	0	---	---
13	Tezel et al. [16]	9	7	---	---	---	2	---
14	Elkhodair et al. [17]	0	0	0	0	0	0	0
15	Elkhodair et al. [17]	1	0	0	0	0	1	0
16	Elkhodair et al. [17]	8	5	0	0	0	3	0
17	Kasmaee et al. [18]	11	8	---	---	---	---	3
18	Das et al. [19]	1	---	---	0	0	---	1
19	Carver et al. [20]	2	0	---	---	---	---	2
20	Kim et al. [21]	2	---	---	0	2	---	0
21	Kim et al. [21]	4	---	---	0	1	---	3
22	Wang. [22]	9	9	---	2	3	---	7
23	Kim et al. [21]	2	---	---	0	2	---	0
24	Eberl et al. [23]	36	---	---	3	10	11	12

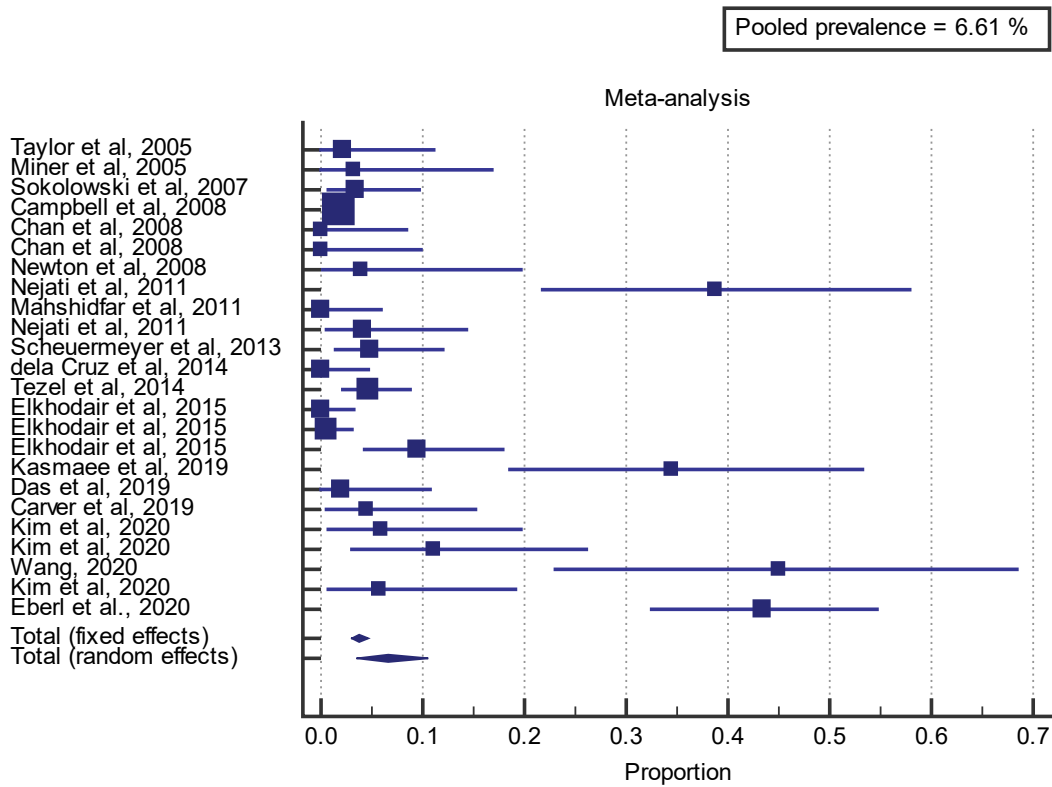


Figure 1: Forest plot demonstrating (Overall adverse events).

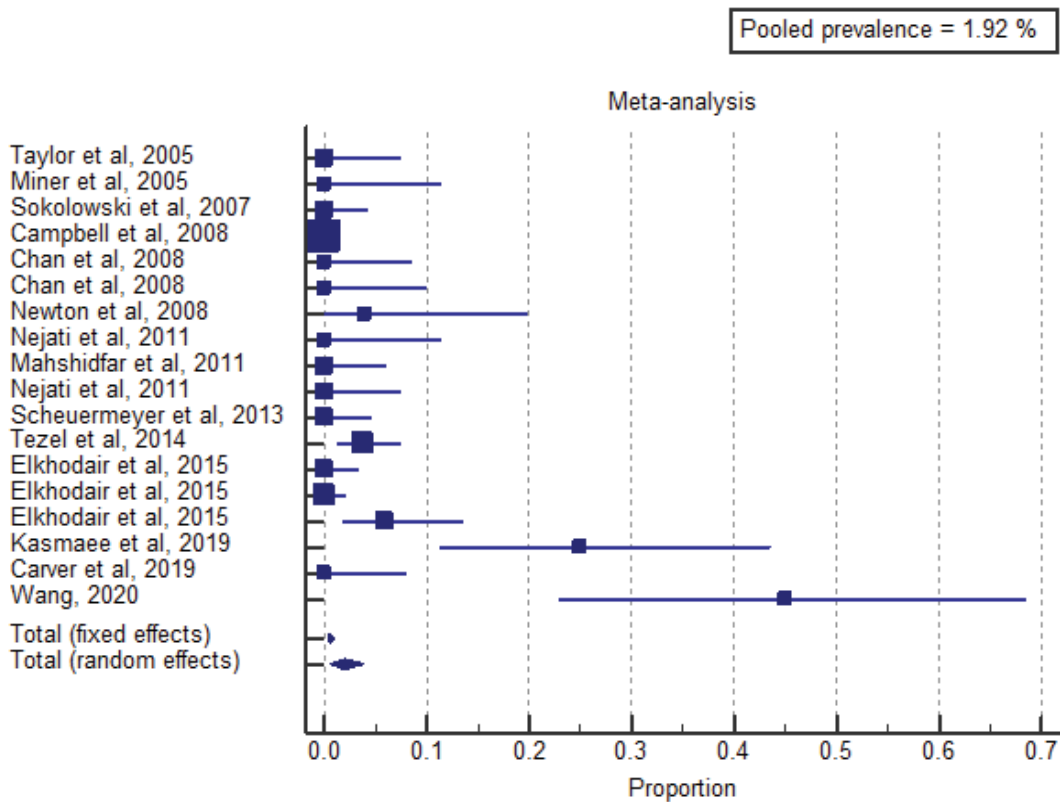


Figure 2: Forest plot demonstrating (Incidence of Agitation).

revealed that, the estimated pooled prevalence of hypotension among adult patients having emergency procedural sedation was (1.71%) (95% CI=0.669 to 3.237) [Figure 5].

I_2 (inconsistency) was 97.6% with a highly significant Q test for heterogeneity ($p < 0.0001$), so the random-effects model was chosen to assess the pooled prevalence.

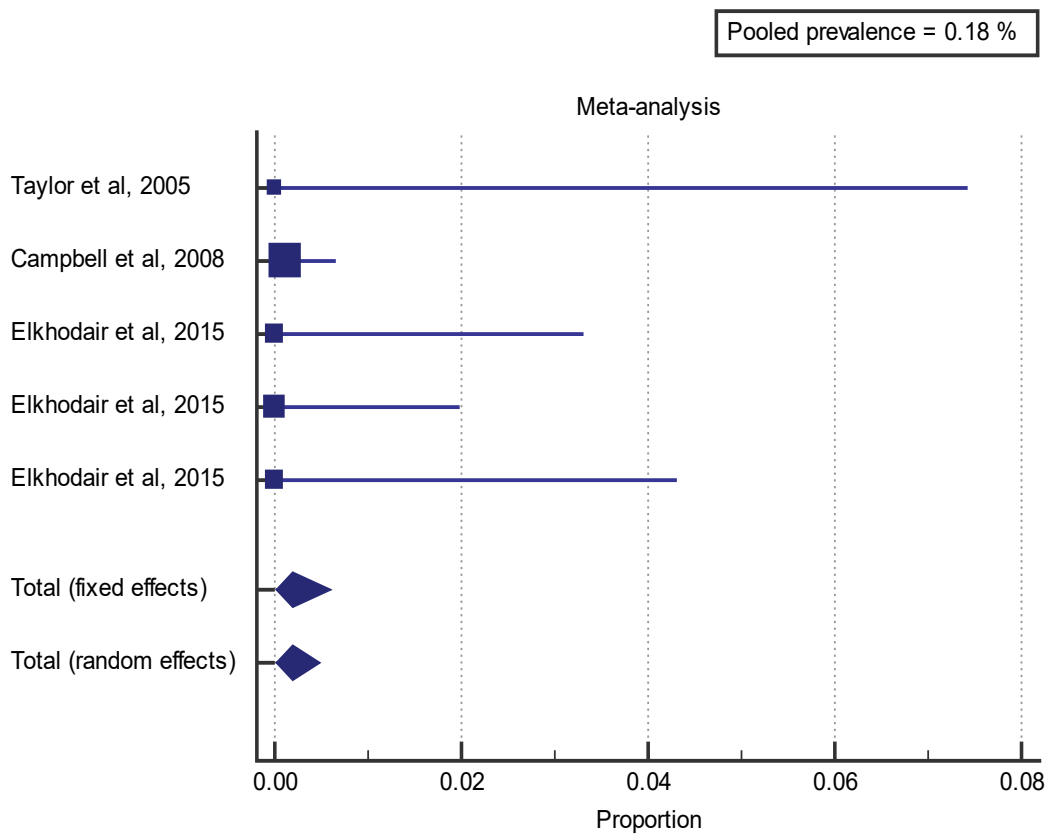


Figure 3: Forest plot demonstrating (Incidence of Aspiration).

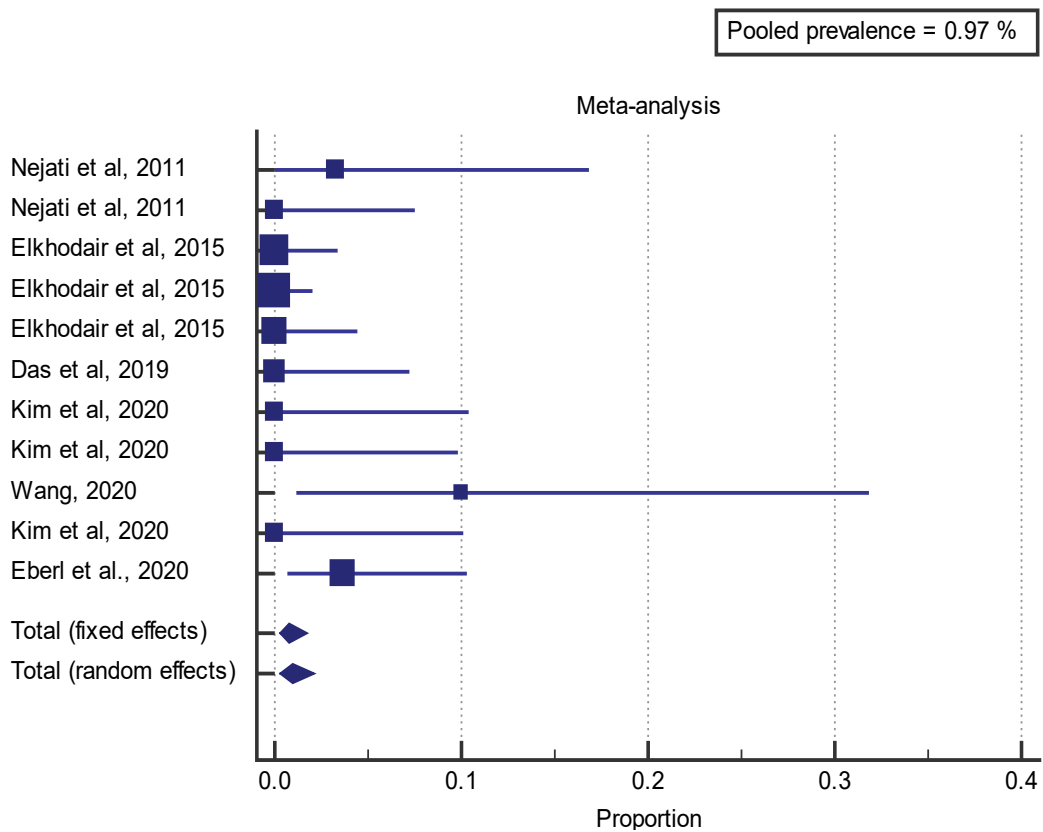


Figure 4: Forest plot demonstrating (Incidence of Bradycardia).

Using the random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of hypoxia among adult patients having emergency procedural sedation was (3%) (95% CI=1.416 to 5.357) [Figure 6].

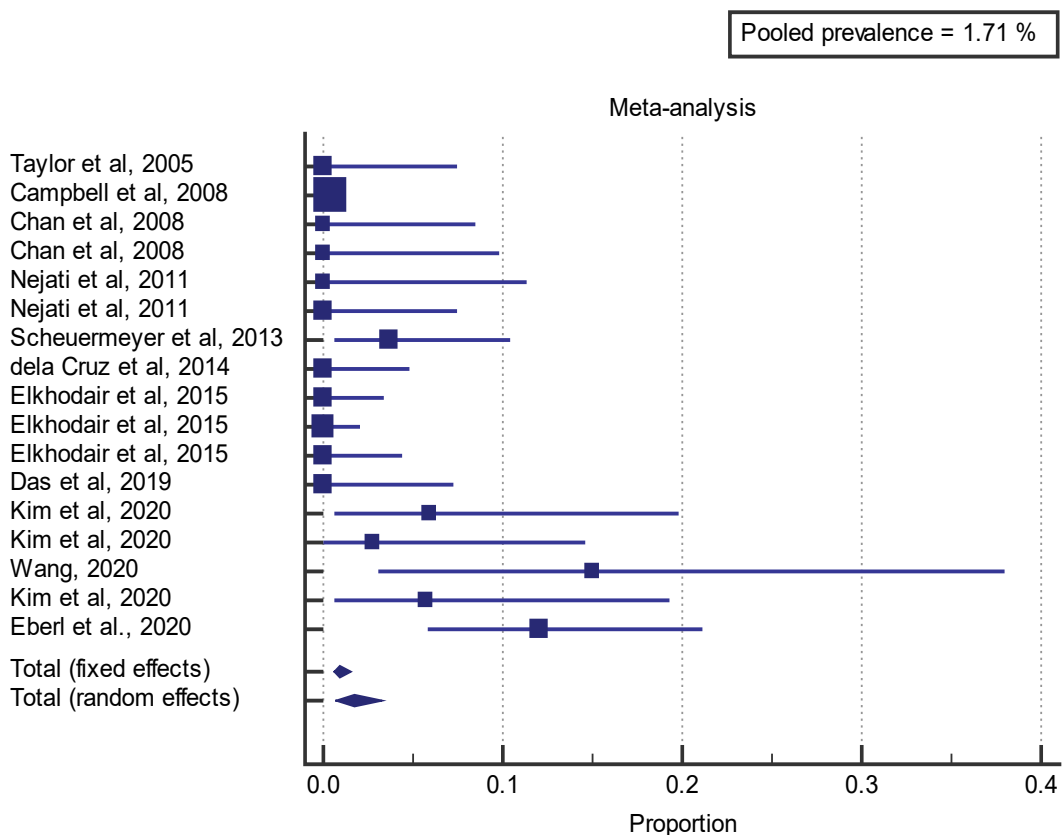


Figure 5: Forest plot demonstrating (Incidence of Hypotension).

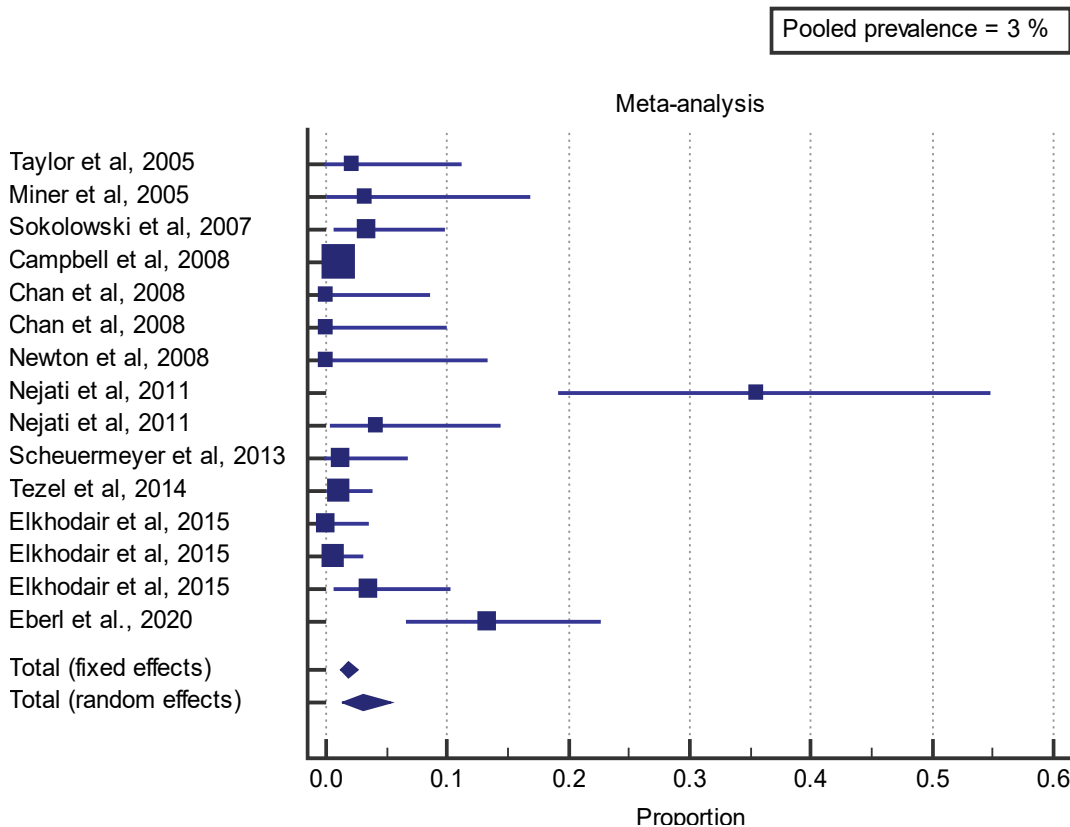


Figure 6: Forest plot demonstrating (Incidence of Hypoxia).

I^2 (inconsistency) was 81% with a highly significant Q test for heterogeneity ($p < 0.0001$), so the random-effects model was chosen to assess the pooled prevalence.

Using the random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of intubation

among adult patients having emergency procedural sedation was (2.18%) (95% CI=0.759 to 4.335) [Figure 7].

Discussion

This work aims to determine the rate of adverse events for adult patients having procedural sedation in the emergency department. The included studies published between 2005 and 2020. Regarding the type of medication used for sedation, we chose 6 studies using each medication (Propofol, Etomidate, Midazolam, and Ketamine) with 24 total studies included [Table 1].

Regarding patients' characteristics, the total number of patients in all the included studies was 2348 patients.

A meta-analysis study was done on 24 studies that described the incidence of adverse events in adult patients having emergency procedural sedation; with an overall number of patients (N=2348).

Concerning the primary outcome measure, we found 24 studies reported adverse events with a total number of patients (N=2348).

Using random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of adverse events among adult patients having emergency procedural sedation was (6.61%) (95% CI=3.558 to 10.534), which came in agreement with Bellolio et al.,^[3] Green et al.,^[24] Taylor et al.^[25] and Smally, Nowicki, and Simelton.^[26]

Bellolio et al. reported that we document the prevalence of

adverse events that occurred during PSA performed in the ED. We included 55 exclusive research comprising nearly 10,000 sedations. The prevalence of severe adverse events requiring emergent interventions including laryngospasm, intubation, or aspiration was low. We did not find any reported deaths in this cohort of sedations inside the emergency department.^[3]

Green et al. reported that, in the large meta-analysis, sub dissociative ketamine (<3 mg/ kg IM) validated fewer airway and respiratory adverse effects relative to complete dissociative dosing; however, such low doses are insufficient for most painful procedures and showed a higher prevalence of recovery agitation.^[24]

Taylor et al. reported that Sedation-associated events in the ED are common even though adverse effects are very uncommon. Respiratory activities are particularly not unusual and are experienced by approximately one-5th of cases. Increasing age and degree of sedation, pre-medication with fentanyl, and sedation with propofol, midazolam or fentanyl are significant risk factors for an airway event.^[25]

Smally, Nowicki, and Simelton reported that, a comprehensive survey of practice variation between emergency medicine practitioners in instructional centers. They discovered a wide spectrum of strategies yet a low rate of adverse events.^[26]

Concerning the secondary outcome measures, using random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of agitation among adult patients having emergency procedural sedation was (1.92%) (95% CI=0.593 to 3.983), which came in agreement with Bellolio et

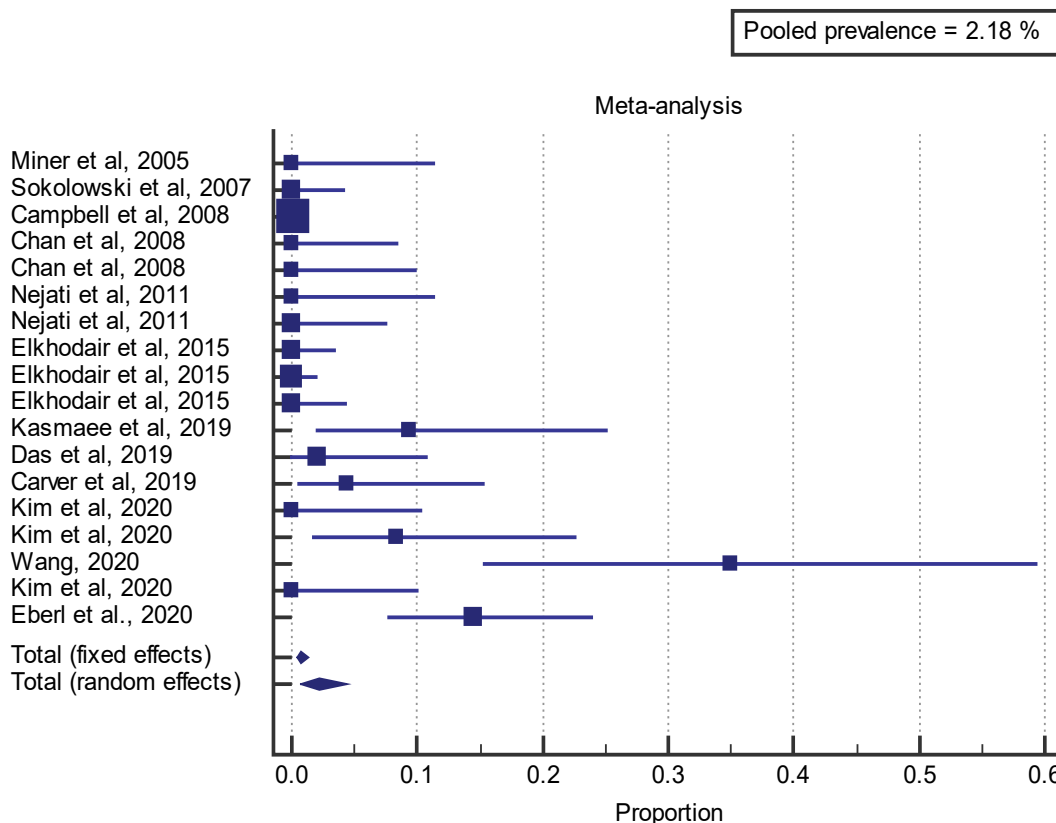


Figure 7: Forest plot demonstrating (Incidence of Intubation).

al.,^[3] Andolfatto and Willman,^[27] Ferguson et al.^[28] and Wakai et al.^[1]

Bellolio et al. reported that a total of 33 researches which includes 6,631 sedations on 6,558 patients reported the outcome of agitation. The prevalence of agitation was 9.8 per 1,000. There had been 25 of 997 patients who obtained medication to treat agitation, with a prevalence of 27.1 per 1,000. Ketamine and ketamine/propofol had the highest fee of agitation. Among the research that used ketamine, the prevalence of agitation was 164.1 per 1,000 sedations and between those receiving ketamine/propofol, 48.1 per 1,000 sedation.^[3]

Andolfatto and Willman reported that a total of 26 patients (3.6% to 4.9%) had recovery agitation, of whom 13 (1.8% to 2.7%) obtained treatment with IV midazolam.^[27]

Ferguson et al. reported that minor agitation (manifesting as procedural interference but not procedural failure) throughout the method was more likely to occur in patients receiving propofol than in those sedated with ketofo.^[28]

Wakai et al. reported that recovery agitation was mentioned in 4 (8.0%) individuals in the propofol group and 17 (36.2%) members in the ketamine group (difference 28.2% to 43.9%). 4 members in the ketamine group required treatment with intravenous midazolam for recovery agitation.^[1]

Using fixed-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of aspiration among adult patients having emergency procedural sedation was (0.18%) (95% CI=0.0247 to 0.489), which came in agreement with Taylor et al.^[25] and Bellolio et al.^[3]

Taylor et al. reported that our case of aspiration is instructive, particularly as she did not vomit and was not administered drugs at risk of causing vomiting. Silent aspiration has been observed for the duration of normal sleep.^[25]

Bellolio et al. reported that a total of 10 researches which includes 2,370 sedations on 2,370 patients mentioned the outcome of aspiration. Aspiration occurred in one case (1.2 per 1,000 sedations) receiving propofol and fentanyl. The case of aspiration was a 65-year-old woman who underwent sedation with fentanyl and propofol for the reduction of an ankle fracture.^[3]

Using the fixed-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of bradycardia among adult patients having emergency procedural sedation was (0.97%), which came in agreement with Bellolio et al.^[3] and Andolfatto and Willman.^[27]

Bellolio et al. reported that a total of 5 researches which includes 837 sedations on 837 sufferers mentioned the outcome of bradycardia. There have been eleven activities of bradycardia (6.5 per 1,000 sedations to 11.8). The prevalence became highest with the usage of etomidate (40.2 per 1,000 sedations, to 70.7) and midazolam/ opiate (32.3 per 1,000 sedations).^[3]

Andolfatto and Willman reported that transient hypotension happened in a 38-year-old patient with a history of IV drug abuse

and hepatitis C who presented at the same time as intoxicated with heroin and cocaine for drainage of a deep cutaneous abscess. Initial BP was 116/80 mm Hg, and the initial heart rate was 133 beats/min. Ketofol PSA was used with 1.5 mg/kg every of ketamine and propofol. a 10-second episode of ventricular tachycardia was documented and BP dropped transiently to 75 /44 mm Hg.^[27]

Using random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of hypotension among adult patients having emergency procedural sedation was (1.71%), which came in agreement with Bellolio et al.,^[3] Ferguson et al.^[28] Hartling et al.^[29] and Hopper et al.^[2]

Bellolio et al. reported that a complete of 27 studies which include 5,801 sedations on 5,801 patients mentioned the outcome of hypotension. The prevalence was 15.2 according to 1,000 sedations. The prevalence became maximum with the usage of propofol (19.1 per 1,000 sedation to 26.3) and midazolam/ opiate (15.4 per 1,000 sedations to 28.8). The forest plot for hypotension.^[3]

Ferguson et al. reported that hypotension was more common in the propofol group with a systolic blood pressure of less than ninety mm Hg being recorded in 7% of the propofol group as compared with only 1% of the ketofol group. However, even though this was statistically significant ($P>.0001$), it did no longer require any intervention beyond a fluid bolus, and so the clinical importance of this finding is doubtful.^[28]

Hartling et al. reported that Propofol is not as effective as ketamine therapy and is associated with more AEs, particularly respiratory events and hypotension than other parental agents.^[29]

Hopper et al. reported that there had been enough data to assess post-administration change in systolic blood pressure (SBP) in 22 visits with a mean pre-administration SBP of 131 6 20 mmHg. Within 4 h of administration, the highest recorded SBP for every patient confirmed a mean growth of 17 6 25 mm Hg from the patient's baseline. the lowest recorded SBP in the same period confirmed a median drop of 14 6 24 mm Hg.^[2]

Using random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of hypoxia among adult patients having emergency procedural sedation was (3%), which came in agreement with Ferguson et al.,^[28] Bellolio et al.,^[3] Hopper et al.,^[2] and Miner et al.^[4]

Ferguson et al. reported that their outcome measure was the prevalence of a respiratory event, described as hypoxia ($SpO_2 <93\%$), hypoventilation (respiration rate <8 breaths/min), apnea (no capnography trace for <15 seconds), laryngospasm or aspiration (persistent hypoxia plus infiltrates on chest radiograph), and the incidence of a rescue intervention elevated oxygen flow rate, airway repositioning/opening, use of an airway adjunct, bag-valve-mask ventilation, or intubation), according to the Quebec criteria.^[28]

Bellolio et al. reported that hypoxia was reported in 42 researches, comprising 373 events in 7,116 sedations on 7,043

patients. The prevalence was 40.2 per 1,000 sedations. The prevalence was maximum with the usage of propofol (19.1 per 1,000 sedation to 26.3) and midazolam/opiate (15.4 per 1,000 sedations to 28.8).^[3]

Hopper et al. reported that twenty-two cases provided oxygen saturation data in which the pre-administration average was 98.6%. Post administration's average highest increase was 1.16%, and the average largest decrease was 0.66%. No patients became hypoxic; the lowest oxygen saturation after administration was 94%.^[2]

Miner et al. reported that two adverse activities have been observed in the 1:1 group. The primary patient developed dystonia during recovery, which resolved with diphenhydramine; there was no airway or respiratory compromise. The second required prolonged observation of 223 minutes after the process; he had required assisted ventilation during the process and had an oxygen saturation nadir of 83%.^[4]

Using random-effects model, the meta-analysis process revealed that, the estimated pooled prevalence of intubation among adult patients having emergency procedural sedation was (2.18%) (95% CI=0.759 to 4.335), which came in agreement with Bellolio et al.^[3] and Green et al.^[24]

Bellolio et al. reported that nineteen researches mentioned the outcome of intubation on 3,636 sedation and 3,636 patients. There had been two intubations (1.6 per 1,000 sedations to 2.9) that occurred in patients that received propofol. One study³⁷ described intubation in an 18-yr-old male with a history of mild allergies who underwent sedation for distal radius fracture. In the course of the sedation, he evolved apnea, hypoxia (nadir SpO₂ of 75%), and emesis. The patient was intubated for 30 minutes. In the 95 mins before sedation, he received morphine, fentanyl, and lorazepam intravenously.^[3]

Green et al. reported that Ketamine-related laryngospasm is uncommon (0.3% in a large meta-analysis²), and the proof supports it as largely idiosyncratic. But clinicians administering ketamine must be prepared to rapidly identify and control this adverse event. Even though a few patients may also require bag-valve-mask ventilation tracheal intubation due to ketamine-related laryngospasm is rare.^[24-29]

Conclusion

To conclude, procedural sedation and analgesia (PSA) are routinely performed in the emergency department (ED) to facilitate potentially painful procedures by alleviating pain, anxiety, and suffering serious adverse events during procedural sedation laryngospasm, aspiration, and intubation are exceedingly rare.

Competing Interests

The authors declare that they have no competing interests. All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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