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Systematic Review

THE USE OF DEXMEDETOMIDINE, MIDAZOLAM, AND KETAMINE IN THE PREVENTION OF EMERGENCE AGITATION IN PEDIATRIC PATIENTS UNDERGOING SURGERY UNDER GENERAL ANESTHESIA

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ABSTRACT

Introduction: Emergence agitation (EA) is a problem that often occurs in pediatric patients during recovery from anesthesia. The cause of EA remained unclear, but the combination of etiologies increases the risk of postoperative agitation. The researchers use various drugs such as ketamine, midazolam, and dexmedetomidine to prevent and treat EA. **Objective:** This review aims to determine the effectiveness of dexmedetomidine, midazolam, and ketamine in preventing emergence agitation in pediatric patients undergoing surgery under general anesthesia. **Method:** This is a systematic review that looks at the outcomes of randomized controlled trials (RCT) studies that tested how well dexmedetomidine, midazolam, and ketamine worked at keeping pediatric patients from becoming agitated during emergence. Literature was collected through Google Scholar and PubMed using the keywords Pediatric, Children, Dexmedetomidine, Ketamine, Midazolam, Emergence Agitation, Emergence Delirium, Postoperative Agitation, and Postoperative Delirium and published within the last ten years (2011–2021) in English or Indonesian. The researchers excluded articles that were not available in full, as well as literature reviews. **Results:** Based on the specified database and keywords identified, there were 695 articles. This literature study included thirteen articles that met the inclusion criteria. Ten articles examined the effectiveness of dexmedetomidine, four reviewed the effectiveness of midazolam, and three examined the effectiveness of ketamine. **Conclusion:** According to the ten reviewed articles, administering dexmedetomidine or ketamine reduced the incidence of emergence agitation in children. However, the administration of midazolam yielded inconsistent results. To evaluate the optimal dosage, route, and timing of dexmedetomidine, midazolam, and ketamine in preventing EA, further studies are necessary.

Keywords: Dexmedetomidine; Emergence Agitation; Ketamine; Medicine; Midazolam; Pediatric

ABSTRAK

Latar belakang: *Emergence agitation* (EA) menjadi salah satu masalah yang sering terjadi pada pasien anak-anak saat pemulihan dari anestesi. Penyebab terjadinya EA belum dapat diketahui dengan pasti, namun kombinasi dari etiologi diduga meningkatkan risiko untuk terjadi agitasi pasca operasi. Berbagai obat digunakan untuk untuk pencegahan maupun pengobatan EA di antaranya ketamine, midazolam, dan dexmedetomidine. **Tujuan:** Tinjauan ini bertujuan untuk mengetahui efektivitas Dexmedetomidine, Midazolam, dan Ketamin pada pencegahan *Emergence Agitation* pada pasien anak yang menjalani pembedahan dengan anestesi umum. **Metode:** Studi ini merupakan tinjauan sistematis yang menelaah hasil penelitian *randomized controlled trial* RCT mengenai efektivitas dexmedetomidine, midazolam, dan ketamin terhadap pencegahan Emergence Agitation pada pasien anak. Pencarian literatur dilakukan melalui basis data Google Scholar dan PubMed dengan kata kunci *Pediatric*, *Children*, Dexmedetomidine, Ketamine, Midazolam, *Emergence Agitation*, *Emergence Delirium*, *Postoperative Agitation*, dan *Postoperative Delirium* yang diterbitkan dalam kurun waktu 10 tahun terakhir (2011 – 2021), menggunakan Bahasa Inggris atau Bahasa Indonesia. Artikel yang tidak bisa didapatkan secara lengkap dan merupakan studi literature review akan dieksklusi. **Hasil:** Berdasarkan database dan keyword yang telah ditetapkan, teridentifikasi 695 artikel. Tiga belas artikel yang memenuhi kriteria inklusi dan dimasukkan dalam studi

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literatur ini. Sepuluh artikel meneliti efektivitas dexmedetomidine, empat artikel menilai efektivitas midazolam, serta tiga artikel meneliti tentang efektivitas ketamin. **Kesimpulan:** Berdasarkan sepuluh jurnal yang telah ditelaah, pemberian dexmedetomidine maupun ketamin dapat menurunkan angka kejadian emergence agitation pada anak, namun hasil yang tidak konsisten dilaporkan pada pemberian midazolam. Studi lebih lanjut diperlukan untuk mengevaluasi dosis, rute, dan waktu pemberian yang optimal dari pemberian dexmedetomidine, midazolam, dam ketamin dalam pencegahan EA.

Kata kunci : *Dexmedetomidine*; *Emergence Agitation*; Ketamin; Midazolam; Obat; Pasien Anak

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INTRODUCTION

Recovery from general anesthesia is a time of physiological stress for many patients. Perioperative morbidity and mortality are higher in children than in adults. One of the complications after anesthesia in pediatric patients is Emergence Agitation (EA), which has been described as the most observed complex of psychomotor perceptual disturbances and agitation in the early post-anesthesia period (1). This is a common problem in pediatric patients recovering from anesthesia. The incident began to appear since the discovery of inhalation agents, and it is estimated to occur around 10–80% globally in the children's population, with the highest range occurring at preschool age (2).

Agitation appears within the first 30 minutes of recovery, lasts about 5–15 minutes, and can go away independently. However, if it is not handled correctly, it can cause various problems for the patient or medical personnel, including the release of the catheter or endotracheal tube, re-bleeding at the operating site, increasing recovery time in the recovery room, and increasing parental concern and anxiety regarding the clinical condition of their children (3).

The cause of EA remains unclear, but a combination of etiologies increases the risk of postoperative agitation. Three major categories present risk factors associated with EA: patient-related, anesthesia-related, and surgery-related. Patient-related risk factors include preschool age and preoperative anxiety (4). Risk factors for EA associated with anesthesia include anesthetic agents and a rapid recovery time. EA risk factors for surgery include ear, nose, throat (ENT), and eye surgical procedures. Patients with high postoperative pain scores frequently report EA events (5). Dysregulation of the dopaminergic, serotonergic, noradrenergic, and GABAergic systems mediates the pathophysiological abnormalities that underlie EA (6).

The majority of nonpharmacological EA prevention focuses on reducing preoperative anxiety. Nonpharmacological intervention is to create an environment with temperature, lighting, a comfortable atmosphere, hypnosis, and music therapy (7). Parents' presence during induction is constantly effective in reducing children's anxiety (8). Ketamine, midazolam, and dexmedetomidine are among the drugs used to prevent and treat EA. Dexmedetomidine is an α2-adrenergic receptor agonist with sedation, anxiolytic, analgesic, and amnesiac effects and does not depress the respiratory system. Various prospective studies have shown that dexmedetomidine can significantly reduce the incidence of EA in pediatric patients after the use of inhalation anesthetics (9). Administration of dexmedetomidine may be accompanied by hemodynamic changes, including a decreased heart rate and decreased blood pressure. The

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sympatholytic effect of dexmedetomidine may be responsible for this (10).

Midazolam is a widely used benzodiazepine premedication agent, particularly in pediatric anesthesia. People believe that midazolam can lower the incidence of EA by lowering the level of pre-operative anxiety (11). There is ongoing debate about the effectiveness of midazolam in reducing risk (12). Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, provides analgesia and sedation with minimal respiratory depression and prevents central sensitization to painful stimulation. Ketamine also works by inhibiting glutamate release (13). This is what makes the authors interested in conducting a study of the effectiveness of dexmedetomidine, midazolam, and ketamine in preventing emergence agitation in pediatric patients undergoing surgery under general anesthesia (14).

METHOD

The research protocol for this literature review uses the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Method. While PRISMA includes flow diagrams for both systematic review and meta-analysis, it's important to note that this study's analysis is exclusively focused on a systematic review approach. The decision to refrain from meta-analysis was due to heterogeneity among included studies in terms of study designs, outcome measures, and population characteristics. Furthermore, the researchers observed limitations in data availability and quality across studies, which made a quantitative synthesis through meta-analysis impractical. Therefore, the researchers performed a narrative synthesis of the findings from the included studies to provide a comprehensive overview and qualitative synthesis of the evidence.The study began with participants, interventions, comparators, outcomes (PICO), research questions (RQ), and criteria used to develop this script. The PubMed and Google Scholar databases were comprehensively reviewed to identify relevant research published between 2011 and 2021 using the keywords that have been determined.

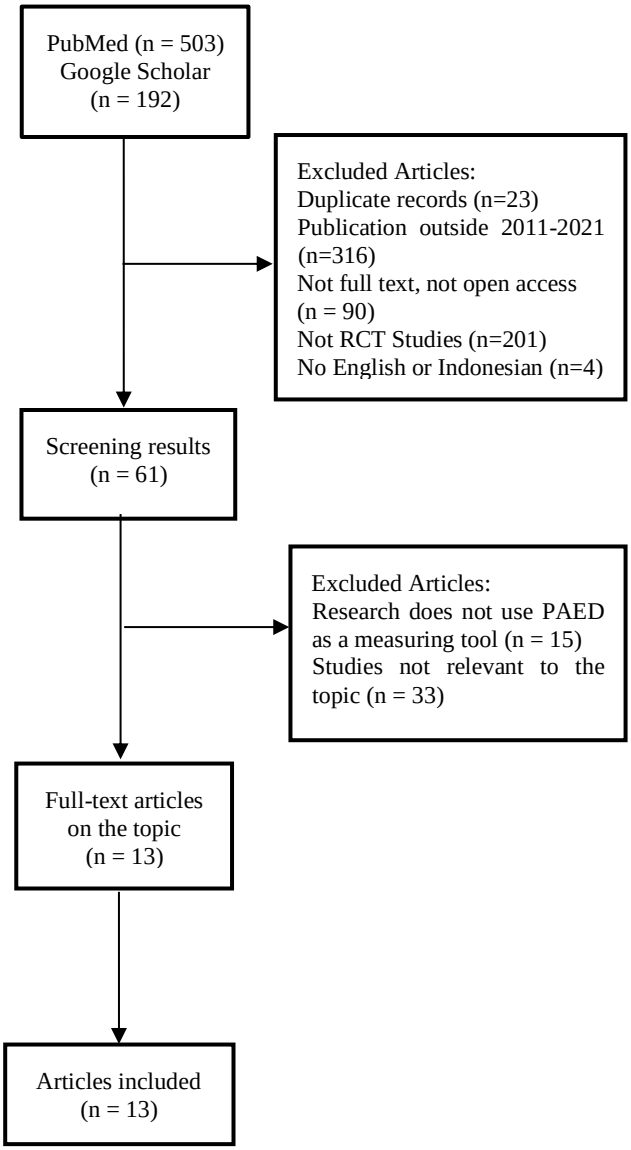

Figure 1. PRISMA flow diagram

Articles were searched with the following keywords: "pediatric," "children," "dexmedetomidine," "ketamine," "midazolam," "emergence agitation," "emergence delirium," "postoperative agitation," "postoperative

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delirium." Studies restricted to randomized controlled trials (RCTs), articles published in English or in Bahasa Indonesia, assessing the effectivity of dexmedetomidine, midazolam, or ketamine compared with placebo or other anesthetic drugs on the incidence of emergence agitation, and involving EA assessment using Pediatric Anesthesia Emergence Delirium (PAED) scales.

Studies without full-text content, observational studies, case series, case reports, correspondence, reviews, and animal studies were excluded. Furthermore, the researchers will screen the obtained articles based on their title and abstract.

Data extraction tools guide the extraction of information from records according to research objectives. The data extracted in each piece if literature includes the primary author, year of publication, sample, number of pieces, surgical procedure, anesthetic drug intervention (time of administration, dose, route of administration), and outcomes of EA.

RESULT AND DISCUSSION

Literature or article searches were carried out through the Pubmed and Google Scholar databases using the keywords 'Pediatric,' 'Children,' 'Dexmedetomidine,' 'Ketamine,' 'Midazolam,' 'Emergence Agitation,' 'Emergence Delirium,' 'Postoperative Agitation,' 'Postoperative Delirium' and found out 695 articles. Then the elimination of articles was carried out using the inclusion and exclusion criteria. The inclusion criteria include the date of publication of the article in the last ten years, starting from 2011 to 2021, in English or Indonesian; the article is primary literature in complete text form; articles discussing the effectiveness of dexmedetomidine, midazolam, and ketamine on preventing the emergence of agitation have been included after reviewing through the titles and abstracts; and there remain 13 articles.

Ten articles discuss the effectiveness of dexmedetomidine in preventing EA.Four articles examined the efficacy of midazolam, and three articles investigated the efficacy of ketamine against EA.

Table 1. Main Characteristics of the Included Studies

Author	Participants	Age	Type of Surgery
Abdelaziz, et al (2016)(15)	105	1 – 7 years	Strabismus
Chen et al. (2013)(16)	78	2 – 7 years	Strabismus
Chen et al. (2018)(17)	100	3-7 years	Inguinal hernia
Hauber, et al (2015)(18)	382	4 – 10 years	Tonsillectomy
Lin et al. (2016)(19)	90	1 – 8 years	Cataract
Makkar, et al (2015)(20)	100	2-8 years	Infra-umbilical
Soliman, et al (2015)(21)	150	4-14 years	Adenotonsillectomy
Begum et al. (2019)(22)	48	2 – 12 years	Abdomen
Bilgen, et al (2014)(23)	78	1 – 8 years	Urology
Ozcan, et al (2014)(24)	62	2 – 7 years	Inguinal hernia repair
Yao et al. (2020)(25)	153	2 – 6 years	Strabismus
Hanna, et al (2018)(26)	80	2 – 9 years	Elective surgery with a minimum duration of 2 hours
Yi et al. (2021)(27)	120	3 – 10 years	Adenotonsillectomy

Dexmedetomidine can reduce the incidence of EA, based on the ten articles reviewed. Previous studies support this. Research conducted by Hendrawan et al. in 2013 showed that dexmedetomidine at a dose

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of 0.2 µg/kgBW could reduce the incidence of delirium while recovering from general anesthesia in pediatric patients. The incidence of agitation was observed in 4.8% of patients receiving an intravenous dexmedetomidine dose of 1 µg/kg, compared to 47.6% in the placebo group (28). One potential explanation is that dexmedetomidine is an α(2)-adrenoceptor agonist with several analgesic, anxiolytic, and sedative properties. Binding to postsynaptic 2 adrenergic receptors at the locus ceruleus mediates its soothing and analgetic effects (29). The mechanism by which dexmedetomidine prevents the occurrence of EA is because dexmedetomidine decreases the secretion of noradrenaline from the locus ceruleus and facilitates the release of inhibitory neurotransmitters, namely GABA.

Table 2. Outcomes of Emergence Agitation

Author	Group	Dosage	Route	Time Administration	Outcomes
Abdelaziz, et al (2016)	DEX Midazolam Placebo	1 mcg/kg 0,1 mg/kg NS	Intranasal Intranasal Infusion	After induction After induction	The incidence of EA DEX (12%)* Midazolam (21%)* Placebo (47%)
Chen et al. (2013)	DEX Ketamine Placebo	1 mcg/kg 1 mg/kg NS	Intravenous Intravenous Infusion	After induction After induction	The incidence of EA DEX (11%)* Ketamine (22%)* Placebo (46%)
Chen et al. (2018)	DEX (D1) DEX (D2) DEX (D3) DEX (D4) Placebo	0.25 mcg/kg 0.5 mcg/kg 0.75 mcg/kg 1 mcg/kg NS	Bolus injection Bolus injection Bolus injection Bolus injection Infusion	After induction After induction After induction After induction	The incidence of EA D1 (5%) D2 (5%) D3 (0%)* D4 (0%)* Placebo (30%)
Hauber, et al (2015)	DEX Placebo	0.5 mcg/kg NS	Bolus injection Infusion	5 min. Before the end of the surgery	The incidence of EA DEX (36%)* Placebo (66%)
Lin et al. (2016)	DEX (D1) DEX (D2) Placebo	1 mcg/kg 2 mcg/kg NS	Intranasal Intranasal Infusion	45 min. before induction 45 min. before induction	The incidence of EA D1 (23,3%)* D2 (10%)* Placebo (80%)
Makkar, et al (2015)	DEX Propofol Placebo	0.3 mcg/kg 1 mg/kg NS	Intravenous Bolus Injection	15 min. before the end of surgery 5 min. Before the end of the surgery	The incidence of EA DEX (9.4%)* Propofol (13.9%) Placebo (40.6%)
Soliman, et al (2015)	DEX Placebo	0.5 mcg/kg + 0,1-0,3 mcg/kg/h NS	Intravenous for 10 min. Infusion	after induction	The incidence of EA DEX (8%)* Placebo (38,66%)
Begum et al. (2019)	DEX (D1) DEX (D2)	0.4 mcg/kg 0.4 mcg/kg/h	Bolus for 10 min. Intravenous	after intubation during surgery	The incidence of EA D1 (20%) D2 (50%)
Bilgen et al. (2014)	Ketamine Alfentanil Placebo	2 mg/kg 10 mcg/kg NS	Intranasal Intranasal Infusion	before induction before induction	The incidence of EA Ketamine (3,8%)* Alfentanil (36%) Placebo (40%)
Ozcan, et al (2014)	Ketamine Midazolam Placebo	0.25 mg/kg 0.03 mg/kg NS	Intravenous Intravenous Infusion	10 min. before the end of surgery 10 min. Before the end of the surgery	PAED scores were similar between the ketamine, midazolam, and control groups

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Continuation of Table 2. Outcomes of Emergence Agitation

Author	Group	Dosage	Route	Time Administration	Outcomes
Yao, et al (2020)	DEX Midazolam Placebo	2 mcg/kg 0.5 mg/kg NS	Intranasal Oral Infusion	45 min. before induction 30 min. before induction	The incidence of EA DEX (11,5%)* Midazolam (44%) Placebo (49%)
Hanna, et al (2018)	Midazolam Zolpidem	0.5 mg/kg 0.25 mg/kg	Oral Oral	Premedication Premedication	The incidence of EA Midazolam (31.58%) Zolpidem (23.81%)
Yi et al. (2021)	DEX (D1) DEX (D2)	0.5 mcg/kg 1 mcg/kg	Intravenous Intravenous	after intubation after intubation	There was no significant difference in the incidence of EA between groups D1 and D2.

A Abbreviation: DEX: dexmedetomidine; NS: normal saline

**p<0,005*

Dexmedetomidine may cause bradycardia or hypotension in some patients, especially when given rapidly by the intravenous route, but intranasal dexmedetomidine has a slower and more gradual onset than intravenous administration (30).

Adults and children commonly use midazolam as a premedication agent to provide anxiolysis, sedation, and amnesia. However, this study's effect on EA was inconsistent. This is in line with previous research. In a study conducted by Cho et al. in 2014, it was reported that intravenous administration of 0.03 mg/kg and 0.05 mg/kg midazolam before the end of surgery can reduce the incidence compared to placebo (31).

In addition, the results of research conducted by Kawai et al. in 2019 stated that giving Midazolam 0,1 mg/kg 30 minutes before the end of the surgical procedure significantly reduces the incidence (12). In contrast, preoperative administration of oral midazolam at a dose of 0.5–1 mg/kg does not reduce the risk of EA because the duration of effective sedation does not last until the postoperative period (11). One explanation is that the fast action of midazolam premedication wears off before the end of the lengthy procedure (13).

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that provides analgesia and sedation with minimal respiratory depression and prevents central sensitization to painful stimulation (13). Providing analgesia and sedation during recovery may be essential factors in reducing the incidence of EA after sevoflurane anesthesia. Ketamine has sedative and amnestic properties, and it exhibits vigorous analgesic activity at subanaesthetic doses (32). This study's results demonstrate that ketamine can lower the incidence of EA, with the exception of surgery, where a caudal block reduces pain (24). Demir et al.'s 2018 research revealed that patients undergoing rhinoplasty surgery who received intravenous 0.5 mg/kg ketamine had a lower EA incidence rate of 8.6% compared to the placebo group's 54.3% (33).

The results of this study have limitations due to factors inherent in the research methodology and the number of articles that specifically address this topic.

SUMMARY

Dexmedetomidine reduces the incidence of post-anesthesia agitation. Intranasal administration is an effective and noninvasive route for administering dexmedetomidine to pediatric patients. Studies of midazolam's effectiveness on the incidence of EA have reported inconsistent findings. One explanation is that the fast action of midazolam

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premedication wears off before the end of the lengthy procedure. Further studies are needed to evaluate the optimal dosage, route, and timing of administration of midazolam for preventing EA. Ketamine significantly reduced the incidence of EA, but adding ketamine to the caudal block under sevoflurane anesthesia showed no further effect on EA.

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Conflict of Interest
There is no conflict of interest.

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Authors' Contributors
All authors have contributed to all processes in this research.

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