International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2024; 7(4): 47-50
Received: 06-08-2024
Accepted: 11-09-2024

Nada Maged Shaheen
Anesthesiology, Department of Surgical Intensive Care and Pain Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Sameh Mohamed Refaat El Shehdawy
Anesthesiology, Department of Surgical Intensive Care and Pain Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Gehan Morsy Eid
Anesthesiology, Department of Surgical Intensive Care and Pain Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Hoda Alsaid Ahmed Ezz
Anesthesiology, Department of Surgical Intensive Care and Pain Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Corresponding Author:
Nada Maged Shaheen
Anesthesiology, Department of Surgical Intensive Care and Pain Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

The role of dexmedetomidine infusion and KETOFOL infusion on the incidence of emergence delirium in children

Nada Maged Shaheen, Sameh Mohamed Refaat El Shehdawy, Gehan Morsy Eid and Hoda Alsaid Ahmed Ezz

DOI: https://doi.org/10.33545/26643766.2024.v7.i4a.512

Abstract
Emergence delirium (ED) represents a disturbance in consciousness that can arise when a child regains awareness following general anesthesia. This condition is characterized by symptoms such as disorientation, increased activity levels, and heightened sensitivity during the early postoperative phase. Studies reveal that the combination of ketamine and propofol, or ketofol, is as beneficial as propofol alone in reducing the incidence of emerging delirium in children receiving sevoflurane anaesthesia for a tonsillectomy. Furthermore, it has been demonstrated that dexmedetomidine lowers the incidence of post-anesthesia emerging delirium in young children.

Keywords: Dexmedetomidine, KETOFOL, children, emergence delirium

Introduction

Postoperative delirium (POD) represents an acute neurological disturbance marked by deviations from a patient's baseline mental function. Rather than being classified as a distinct disease, POD encompasses a range of symptoms that include alterations in consciousness, attention, cognition, and perception. Typically, the onset of POD occurs between 2 to 5 days following surgery [1].

Ketofol, a ketamine and propofol combination, has attracted a lot of interest as a potential analgesic and procedural sedative due to its capacity to preserve more stable respiratory and haemodynamic parameters. This is attributed to the opposing effects of ketamine, which has sympathomimetic properties, and propofol, this may result in respiratory depression and dose-dependent hypotension. Ketofol is used in a range of mixed ratios, from 1:1 to 1:10 [2].

Dexmedetomidine is a highly selective α2-adrenoreceptor agonist that has been widely used in surgical settings because of its advantageous analgesic, sedative, and anxiolytic qualities. By activating α2 receptors and stimulating the vagus nerve through a mechanism dependent on vagal and α7 nicotinic acetylcholine receptors, DEX not only provides analgesia but also reduces the use of medications that may induce delirium, promotes natural sleep-wake cycles, and mitigates inflammatory responses. As such, it's considered a potentially effective treatment approach for delirium prevention and control in intensive care units [3].

In paediatric anaesthesia, emergent delirium (ED) is defined as a disturbance in a child's awareness or attention to their environment that happens right after anaesthesia. It is also accompanied by disorientation and perceptual abnormalities, such as hypersensitivity to stimuli and hyperactive motor behaviour [4].

The reported incidence of ED varies widely, ranging from 2% to 80%, with a general consensus indicating that approximately 10% to 30% of children experience this phenomenon in the post-anesthesia care unit (PACU) [5].

Children identified as being at elevated risk for experiencing various clinical phenomena tend to exhibit characteristics such as youthfulness, heightened emotional responses, impulsivity, and reduced social engagement. Furthermore, their parents display significantly increased levels of anxiety both in the preoperative holding area and during the process of separation [6].

Cause and Risk factors

- **Patient Risk Factors:** The existence of preexisting anxiety or maladaptive behaviors has been identified as a major contributor to the likelihood of developing emergence delirium (ED). This includes behaviors such as agitation, uncooperativeness, pronounced expressions of anger (e.g., temper tantrums), and limited adaptability skills [7].
- **Surgical Risk Factors:** Certain surgical interventions have been correlated with a heightened risk of ED. Notably, surgeries related to the ear, nose, and throat exhibit the highest rates of ED, followed by abdominal, orthopedic, and urologic procedures [7].
- **Anesthetic Risk Factors:** The administration of volatile anesthetics has been significantly linked to the onset of ED. Agents such as isoflurane, sevoflurane, halothane, and desflurane have all been implicated in this phenomenon, with sevoflurane showing the highest incidence of ED, likely due to its frequent use in research studies. Additionally, rapid emergence from anesthesia has been recognized as a potential contributing factor [7].

The abrupt awakening in an unfamiliar setting surrounded by strangers can exacerbate the patient's inherent fears, leading to ED [8].

Postoperative pain can complicate the assessment of ED, as it can be challenging, particularly in nonverbal children, to distinguish between pain and delirium. When pain is excluded as a factor, the likelihood of diagnosing ED increases, especially when positive scores are recorded on the Pediatric Anesthesia Emergence Delirium (PAED) scale [9].

A child's failure to establish eye contact while being unaware of their surroundings is more indicative of ED. Conversely, abnormal facial expressions, crying, and inconsolability in a child who is making eye contact and is aware of their environment are more likely attributable to pain. In instances where pain and ED cannot be clearly differentiated, pain should be prioritized as a consideration [9].

Prevention

- **Reducing or avoiding risk factors:** The established correlation between preoperative and intraoperative factors in the occurrence of emergence delirium (ED) suggests that there may be advantages in adjusting anesthesia techniques for children identified as being at the highest risk. This could involve minimizing or eliminating exposure to volatile anesthetics or incorporating medications that can influence postoperative behavior. By employing such an approach, it is possible to completely avoid the use of sevoflurane or restrict it to a brief period of gaseous induction until intravenous (i.v.) access is achieved [10].
- **Pharmacological treatment:** Pharmacological interventions for emergence delirium typically resolve spontaneously; however, both pharmacological and non-pharmacological strategies are available for treatment and prevention [10]. These include:

- Total intravenous anesthesia (TIVA) with propofol at the conclusion of surgery
- Administration of midazolam either orally or intravenously at the end of the surgical procedure
- Clonidine given orally preoperatively or intravenously during the intra- or postoperative period
- Dexmedetomidine administered intravenously in the preoperative or intraoperative phases
- Fentanyl delivered intravenously or intranasally during surgery
- Ketamine provided intranasally preoperatively or via intravenous/intrathecal routes
- Magnesium infusion administered intravenously during surgery
- Dexamethasone given intravenously or preoperatively
- Gabapentin taken orally in the preoperative phase

- **Regional Anesthesia**
  It has been demonstrated that using a preoperative caudal block in the setting of regional anaesthesia can dramatically reduce the rate of ED in paediatric patients having inguinal hernia repairs [11].
- **Non-pharmacologic Interventions**
  Non-pharmacological strategies aimed at preventing emergence-delirium have primarily concentrated on alleviating preoperative anxiety. A substantial body of research has emerged regarding the predictors of anxiety in children prior to surgery and methods for its mitigation [12].

Ketofol, a ketamine and propofol combination, is proposed as an improved anaesthetic agent for quick, painful operations since it can lessen the side effects of each drug alone. Propofol and ketamine are both often used for procedural sedation and analgesia (PSA), with ketamine offering the advantages of maintaining cardiac and respiratory stability while also providing analgesic effects [13].

Although propofol doesn't have analgesic qualities, its early start and short duration of action help with faster recovery periods. Moreover, propofol has been linked to a higher risk of cardiovascular depression and apnoea. Ketofol appears to be a good substitute for procedural analgesia and sedation (PSA)**,** aiming to harness the advantages of both constituent drugs while mitigating potential adverse effects. Although existing literature presents inconclusive findings regarding ketofol's efficacy, the majority indicates that it is a safe, effective, and well-tolerated combination, with risks comparable to those of the individual agents [13].

Both propofol and ketamine have been successfully utilized in isolation to manage emergence agitation in both adults and pediatric populations. The combination of ketamine and propofol, referred to as "ketofol," has been suggested as an effective strategy for preventing emergence agitation in pediatric patients undergoing straightforward surgical procedures, while also providing enhanced hemodynamic stability [14].

Studies show that the combination of propofol and ketofol lowers the incidence of emerging delirium in children receiving sevoflurane anaesthesia for a tonsillectomy with an effectiveness that is on par with propofol alone. This combination guarantees haemodynamic stability, favourable recovery metrics, and appropriate postoperative sedation and analgesia. Additionally, ketofol has been shown to provide superior analgesic effects in the immediate postoperative phase [14].

Ketamine added to propofol caused a delay in recovery, according to a simulation research on ketofol dosage in

paediatric anaesthesia using McFarlan's manual infusion regimen. Consequently, for mixes containing 1:10 of ketofol, respectively, the infusion rates were changed to 90%. Ketofol ratios of 1:10 may be useful for brief anaesthesia without lengthening recovery periods [15].

A pleasant postoperative phase may be ensured by TIVA with a 1:10 ratio of ketofol admixture and a decrease to 90% of the McFarlan dosing regimen, which is easily manufactured. Nonetheless, given the closeness of the results, this study indicates a statistical relevance for the duration of extubation and hospital stay. Additionally, during short-term paediatric surgery, decreased infusions of ketofol at ratios of 1:10 offer haemodynamic stability, effective recovery, and postoperative analgesia [16].

Dexmedetomidine

Respiratory depression is prevented while anxiolysis and cooperative sedation are facilitated by the highly selective α2 adrenergic agonist dexmedetomidine. It has analgesic effects that may be described as opioid-sparing and reduces sympathetic outflow from the central nervous system (CNS) in a dosage-dependent manner. Emerging research indicates that dexmedetomidine may confer organ protective benefits against ischemic and hypoxic damage, including cardioprotective, neuroprotective, and renoprotective effects [17].

Although dexmedetomidine is approved solely for intravenous administration, various alternative routes have been explored. Extravascular administration can mitigate the pronounced peak plasma concentrations typically associated with intravenous use. Following oral administration, a significant first-pass metabolism occurs, resulting in a bioavailability of approximately 16%. The drug is effectively absorbed via the intranasal and buccal mucosa, which may be advantageous in managing uncooperative pediatric or geriatric patients [18].

The sedation induced by dexmedetomidine closely resembles natural sleep, particularly the deep restorative sleep that follows periods of sleep deprivation. It is most likely responsible for its sedative and hypnotic effects by blocking norepinephrine release from the locus ceruleus. Gamma-aminobutyric acid (GABA) and galanin are released when the ventrolateral preoptic nucleus (VLPO) lacks inhibitory regulation, further suppressing the locus ceruleus and the tuberomammillary nucleus (TMN). This cascade of inhibitory responses also results in reduced histamine release, contributing to the hypnotic effect [19].

In the realm of sedation within the intensive care unit (ICU), the typical dosage range is established between 0.2 to 0.7 µg/kg per hour. However, this dosage may be increased to 1.5 µg/kg per hour to attain the necessary sedation level. Although doses as high as 2.5 µg/kg per hour have been documented, it is widely accepted that exceeding 1.5 µg/kg per hour does not yield further therapeutic benefits and may lead to a rise in adverse effects [20].

Numerous studies have emerged regarding the application of dexmedetomidine for sedation in both noninvasive and invasive procedures involving young patients [21].

Furthermore, dexmedetomidine has been employed to mitigate agitation in the pediatric demographic and facilitate intubation in sedated pediatric patients within the postanesthesia care unit following sevoflurane anesthesia [22].

Conclusion

Emergence delirium (ED) is a prevalent postoperative issue among pediatric patients, marked by symptoms like disorientation and heightened sensitivity shortly after regaining consciousness. Various factors, including pre-existing anxiety, certain types of surgeries, and volatile anesthetics like sevoflurane, contribute significantly to ED. Both pharmacological and non-pharmacological strategies are employed to reduce the incidence of ED. The combination of ketamine and propofol, known as ketofol, has shown potential in managing ED by providing hemodynamic stability and effective sedation. Similarly, dexmedetomidine, an α2-adrenergic agonist, is beneficial for its sedative and analgesic properties, reducing postoperative agitation and promoting stable recovery. Tailoring anesthetic approaches based on risk factors, using sedatives like ketofol and dexmedetomidine, and addressing preoperative anxiety can collectively reduce the occurrence of ED and improve pediatric postoperative outcomes.

Acknowledgement

Not available.

Author's Contribution

Not available.

Conflict of Interest

Not available.

Financial Support

Not available.

References

1. Wei W, Zhang A, Liu L, Zheng X, Tang C, Zhou M, *et al*. Effects of subanaesthetic S-ketamine on postoperative delirium and cognitive function in elderly patients undergoing non-cardiac thoracic surgery: a protocol for a randomised, double-blinded, placebo-controlled and positive-controlled, non-inferiority trial (SKED trial). BMJ Open. 2022;12.
2. Ali I, Alahdal M, Xia H, Moughrabi ASE, Shiqian H, Yao S, *et al*. Ketofol performance to reduce postoperative emergence agitation in children undergoing adenotonsillectomy. Libyan J Med. 2020;15:78.
3. Abd Ellatif SE, Mowafy SMS, Shahin MA. Ketofol versus Dexmedetomidine for preventing postoperative delirium in elderly patients undergoing intestinal obstruction surgeries: A randomized controlled study. BMC Anesthesiology. 2024;24:1.
4. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology. 2004;100:1138-1145.
5. Reduque LL, Verghese ST. Paediatric emergence delirium. BJA Education. 2013;13:39-41.
6. Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, *et al*. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg. 2004;99:1648-1654.
7. Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg. 2003;96:1625-1630.
8. Kennedy RM. Sedation in the Emergency Department:

A Complex and Multifactorial Challenge. Pediatric Sedation Outside of the Operating Room: A Multispecialty International Collaboration. 2021. p. 413-473.
9. Somaini M, Engelhardt T, Fumagalli R, Ingelmo P. Emergence delirium or pain after anaesthesia—how to distinguish between the two in young children: A retrospective analysis of observational studies. Br J Anaesth. 2016;116:377-383.
10. Nair S, Wolf A. Emergence delirium after paediatric anaesthesia: new strategies in avoidance and treatment. BJA Education. 2018;18:30-33.
11. Aouad M, Kanazi G, Siddik-Sayyid S, Gerges F, Rizk L, Baraka A, *et al*. Preoperative caudal block prevents emergence agitation in children following sevoflurane anesthesia. Acta Anaesthesiol Scand. 2005;49:300-304.
12. Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. Curr Opin Anesthesiol. 2014;27:309-15.
13. Iqbal AU, Shuster ME, Baum CR. Ketofol for procedural sedation and analgesia in the pediatric population. Pediatr Emerg Care. 2022;38:28-33.
14. Rizk SN, Samir EM. Use of ketofol to control emergence agitation in children undergoing adenotonsillectomy. Egypt J Anaesth. 2014;30:13-19.
15. Coulter FL, Hannam JA, Anderson BJ. Ketofol simulations for dosing in pediatric anesthesia. Paediatr Anaesth. 2014;24:806-812.
16. Biricik E, Karacaer F, Güleç E, Sürmelioğlu Ö, Ilgınel M, Özcengiz D, *et al*. Comparison of TIVA with different combinations of ketamine–propofol mixtures in pediatric patients. Journal of Anesthesia. 2018;32:104-111.
17. Panzer O, Moitra V, Sladen RN. Pharmacology of sedative-analgesic agents: Dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. Critical Care Clinics. 2009;25:451-469.
18. Weerink MA, Struys MM, Hannivoort LN, Barends CR, Absalom AR, Colin P, *et al*. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clinical Pharmacokinetics. 2017;56:893-913.
19. Nelson LE, You T, Maze M, Franks N. Evidence that the mechanism of hypnotic action in dexmedetomidine and muscimol-induced anesthesia converges on the endogenous sleep pathway. Anesthesiology. 2001;95:68-72.
20. Koyyalamudi V, Sen S, Patil S, Creel JB, Cornett EM, Fox CJ, *et al*. Adjuvant agents in regional anesthesia in the ambulatory setting. Current Pain and Headache Reports. 2017;21:01-10.
21. Afonso J, Reis F. Dexmedetomidine: Current role in anesthesia and intensive care. Revista Brasileira de Anestesiologia. 2012;62:125-133.
22. Ard J, Doyle W, Bekker A. Awake craniotomy with dexmedetomidine in pediatric patients. Journal of Neurosurgical Anesthesiology. 2003;15:263-266.

How to Cite This Article
Shaheen NM, Shehdawy SMRE, Eid GM, Ezz HAA. The role of dexmedetomidine infusion and KETOFOL infusion on the incidence of emergence delirium in children. International Journal of Medical Anesthesiology. 2024;7(4):47-50.