JPPT | Case Report

General Anesthesia With Dexmedetomidine and Remifentanil in a Neonate During Thoracotomy and Resection of a Congenital Cystic Adenomatoid Malformation

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Based on animal data, concern has been expressed regarding the potential deleterious neurocognitive effects of general anesthesia during infancy and early life. Although there are no definitive data to prove this effect, the neonatal period has been suggested to be the most vulnerable period. While various inhaled and intravenous anesthetic agents have been implicated, dexmedetomidine and the opioids may be devoid of such effects. However, there are limited data regarding the combination of these agents during neonatal surgery and anesthesia. We present the use of these agents in combination with epidural anesthesia for postoperative analgesia in a 1-day-old neonate during thoracotomy and excision of a congental cystic adenomatoid malformation. Previous reports of the use of this unique combination of agents are reviewed and their role in this scenario discussed.

Introduction

Animal data have suggested that there may be longer-term deleterious neurocognitive effects of general anesthesia during infancy and early life.[1–6] Although the exact implications of this effect have yet to be proven, media attention has been raised and many parents are aware of the potential for such problems.[7,8] The potential neurocognitive effects of various general anesthetic agents have been demonstrated in laboratory animals and suggested from retrospective clinical trials.[1–6] The anesthetic agents identified as possible neurotoxins include either γ-amino-butyric-acid agonists including the volatile anesthetic agents, benzodiazepines, barbiturates, and propofol or N-methyl-D-aspartate antagonists such as nitrous oxide or ketamine. Although spinal and regional anesthesia are acceptable alternatives and have seen increased use in an attempt to eliminate the concerns of such problems, many surgical procedures may not be amenable to regional anesthesia.[9,10]

We report the case of a neonate who presented for excision of a congenital cystic adenomatoid malformation during the first day of life. General anesthesia was provided by using a combination of dexmedetomidine and remifentanil. Previous reports of the use of this unique combination of agents are reviewed and its potential role in this scenario discussed.

Case Report

Institutional Review Board approval is not required for presentation of single case reports at Nationwide Children's Hospital, Columbus, Ohio. A 1-day old, 3.3-kg full-term female infant with prenatally diagnosed congenital lobar emphysema presented to the operating room for left thoracotomy immediately after delivery. Given the severity of the lesion and the potential for immediate respiratory compromise, the infant was delivered in an operating room at our Children's Hospital. The cesarean section for delivery was uneventful and there were no other medical issues. The patient initially had a good respiratory effort, but subsequent chest radiograph demonstrated a mediastinal shift and the infant was transported to the operating room. Physical examination was unremarkable and the vital signs were stable except for tachypnea. An umbilical arterial and venous cannula had been placed after delivery. Routine American Society of Anesthesiologists' monitors were placed and the infant was positioned on a shoulder roll to optimize airway positioning. Following pretreatment with atropine (0.1 mg), anesthesia was induced with fentanyl (4 µg/kg) and neuromuscular blockade provided by rocuroniuim (1 mg/kg). The trachea was intubated with a 3.0-mm cuffed endotracheal tube by using rapid sequence technique and a Miller 1 blade. A 22-gauge peripheral intravenous cannula was placed in the left

hand. The endotracheal tube was advanced into the right main stem bronchus for lung isolation. After the endotracheal tube was secured and 1 lung-ventilation was confirmed, the patient was placed on pressure-controlled ventilation with a peak inflating pressure of 18 to 22 cm H_2O. Maintenance anesthesia was provided by infusions of dexmedetomidine and remifentanil. The dexmedetomidine infusion included a 1 µg/kg loading dose followed by an infusion at 1 µg/kg/hr and was titrated down to 0.4 µg/kg/hr after 20 minutes. The remifentanil infusion was started at 0.1 µg/kg/min and titrated up to 0.4 µg/kg/min. Intraoperative heart rate (HR) and blood pressure were maintained within 20% of preoperative values. The patient's baseline HR was 150 to 160 beats/min. At the start of the case, atropine was administered and the HR increased to 180 to 190 beats/min. The HR remained elevated for the initial 1 hour of the case. After this time, there was a gradual decrease back to baseline. The patient had a baseline mean arterial pressure of 40 mm Hg. During intraoperative care, the remifentanil infusion was titrated to maintain the mean arterial pressure in the 40 to 50 mm Hg range. After the procedure was completed, the dexmedetomidine infusion was discontinued while the remifentanil infusion was continued during placement of a caudal epidural catheter, which was threaded to the thoracic level with ultrasound guidance. Dosing included a loading dose of 1.5% chloroprocaine followed by a continuous infusion, using our previously described technique.[11] The remainder of the intraoperative course was uneventful. The patient was transferred to the Neonatal Intensive Care Unit with the endotracheal tube in place with spontaneous ventilation. The following afternoon, the patient's trachea was extubated. The epidural infusion was continued for 72 postoperative hours to provide analgesia. The remainder of his postoperative course was uneventful.

Discussion

The techniques of neonatal surgery continue to advance, thereby resulting in more complex surgical procedure in younger and critically ill neonates. In addition to concerns regarding prematurity, size, and comorbid conditions, the recent literature has suggested that various anesthetic agents may impact future neurocognitive function.[7,8] Although there is persistent controversy regarding these issues with recent clinical trials demonstrating the absence of neurocognitive deficits effect following a brief exposure to sevoflurane (less than 60 minutes), parental concerns and ongoing uncertainty have pushed anesthesia providers to consider alternative regimens and techniques.[10,12]

Dexmedetomidine is an α_2-adrenergic agonist that initially received approval by the United States Food & Drug Administration (FDA) in 1999 for the sedation of adults during mechanical ventilation with subsequently received FDA approval for monitored anesthesia care

in 2009. Although only FDA approved for use in adults, dexmedetomidine has been shown to be efficacious in several different clinical scenarios in infants and children, including sedation during mechanical ventilation, procedural sedation, supplementation of postoperative analgesia, prevention of emergence delirium, and treatment of withdrawal.[13] The current literature suggests that dexmedetomidine may have limited apoptotic effects and may in fact limit the proapoptotic effects of other anesthetic agents.[14,15] It is still unknown if the data from animal studies can be applied to humans; however, using a combination of medications such as dexmedetomidine and remifentanil may offer an alternative to other conventional agents that have proapoptotic effects in animal studies and the theoretical potential for negative effects on long-term neurocognitive outcome.

Remifentanil is unique in that doses can be escalated to effectively provide intense analgesia and anesthesia during major surgical procedures while allowing for a rapid emergence given its pharmacokinetic profile.[16] Its metabolism by non-specific esterases results in a half-life of 5 to 8 minutes even in neonates and infants.[17] While there is literature describing the clinical use of remifentanil and dexmedetomidine separately in neonates, there are no previous case reports of the use of these two agents in combination as the primary anesthetic in a newborn. Outside of the neonatal period, anecdotal experience has been reported with the combination of these two agents in various clinical scenarios including patients with comorbid conditions and absolute or relative contraindications to the use of the volatile anesthetic agents.[18–21]

In our patient, the titration of these two agents provided effective intraoperative anesthesia with effective control of intraoperative hemodynamic variables in response to the surgical stimulus. Dosing for dexmedetomidine included a loading dose of 1 µg/kg followed by an infusion starting at 1 µg/kg/hr, which was then titrated down to 0.4 µg/kg/hr after 20 minutes. The remifentanil infusion was started at 0.1 µg/kg/min and titrated up to 0.4 µg/kg/min as needed during surgical stimulation. Given its shorter half-life, bolus dosing of remifentanil is not generally required. While the rapid dissipation of its effects permit rapid awakening from anesthesia, the analgesic effects also dissipate, thereby mandating an alternative form of postoperative analgesia, hence the use of epidural analgesia in our patient.

The most common adverse effects of remifentanil and dexmedetomidine, whether used alone or in combination, are bradycardia and hypotension. The incidence and magnitude of these problems can be minimized by slow titration of the infusions and treatment with an anticholinergic agent such as atropine or the administration of fluid. One adverse effect that is unique to the synthetic opioids when compared to other agents is chest wall or laryngeal rigidity.[22] Chest wall rigidity occurs more commonly with large doses

and rapid administration. Clinical manifestations include coughing, hypoxemia, and difficult bag-valve-mask ventilation. These issues are of concern only when synthetic opioids are administered without a neuromuscular blocking agent.

Surgery in the neonatal population may be unavoidable. Limiting the amount of time that the neonate or infant is exposed to anesthesia is generally the goal, given the uncertainty surrounding the long-term effects on their neurocognitive function; however, the inherent difficulties of neonatal surgery must be considered when formulating a safe and effective anesthetic plan. Alternatively, animal studies have demonstrated the potential safety of dexmedetomidine and remifentanil with no proapoptotic effects. The successful clinical use of dexmedetomidine and remifentanil in a patient undergoing a major surgical procedure supports its use in this and other clinical situations. The combination of these mediations allows for a hemodynamically stable anesthetic with excellent analgesia, while simultaneously taking advantage of the neuroprotective benefits of dexmedetomidine.

ARTICLE INFORMATION

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REFERENCES

1. Sun L. Early childhood general anaesthesia exposure and neurocognitive development. *Br J Anaesth.* 2010;105(S1):i61–i86.
2. Blaylock M, Engelhardt T, Bissonnette B. Fundamentals of neuronal apoptosis relevant to pediatric anesthesia. *Paediatr Anaesth.* 2010;20(5):383–395.
3. Mellon RD, Simone AF, Rappaport BA. Use of anesthetic agents in neonates and young children. *Anesth Analg.* 2007;104(3):509–520.
4. Loepke AW, Soriano SG. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. *Anesth Analg.* 2008;106(6):1681–1707.
5. Istaphanous GK, Loepke AW. General anesthetics and the developing brain. *Curr Opin Anaesthesiol.* 2009;22(3):368–373.
6. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci.* 2003;23(3):876–882.
7. Weiss M, Bissonnette B, Engelhardt T, Soriano S. Anesthetists rather than anesthetics are the threat to baby brains. *Paediatr Anaesth.* 2013;23(10):881–892.
8. Davidson AJ. Anesthesia and neurotoxicity to the developing brain: the clinical relevance. *Paediatr Anaesth.* 2011;21(7):716–721.
9. Davidson AJ, Morton NS, Arnup SJ, et al; General Anesthesia Compared to Spinal Anesthesia (GAS) Consortium. Apnea after awake regional and general anesthesia in infants: The General Anesthesia Compared to Spinal Anesthesia Study—comparing apnea and neurodevelopmental outcomes, a randomized controlled trial. *Anesthesiology.* 2015;123(1):38–54.
10. Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet.* 2016;387(10015):239–250.
11. Veneziano G, Iliev P, Tripi J, et al. Continuous chloroprocaine infusion for thoracic and caudal epidurals as a postoperative analgesia modality in neonates, infants and children. *Pediatr Anesth.* 2016;26(1):84–91.
12. Sun LS, Li G, Miller TLK, et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. *JAMA.* 2016;315(21):2312–2320.
13. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. *Pediatr Crit Care Med.* 2007;8(2):115–131.
14. Wei Y, Hu J, Liang Y, et al. Dexmedetomidine pretreatment attenuates propofol-induced neurotoxicity in neuronal cultures from the rat hippocampus. *Mol Med Rep.* 2016;14(4):3413–3420.
15. Wang X, Zhao B, Li X. Dexmedetomidine attenuates isoflurane-induced cognitive impairment through antioxidant, anti-inflammatory and anti-apoptosis in aging rat. *Int J Clin Exp Med.* 2015;8(10):17281–17285.
16. Kamata M, Tobias JD. Remifentanil: applications in neonates. *J Anesth.* 2016;30(3):449–460.
17. Ross AK, Davis PJ, Dear GL, et al. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg.* 2001;93(6):1393–1401.
18. Moharir A, Tobias JD. Monitored anesthesia care with dexmedetomidine and remifentanil during cardiac catheterization in a patient with Duchenne muscular dystrophy and malignant hyperthermia susceptibility. *Anaesth Pain Intensive Care.* 2013;17:292–295.
19. Burnett T, Schwartz L, Tobias JD. Anesthesia with dexmedetomidine and remifentanil in a child with a mitochondrial myopathy. *South Afr J Anaesth Analg.* 2011;17:262–264.

20. Walia H, Whitaker E, Pearson G, Tobias JD. General anesthesia with dexmedetomidine and remifentanil in a 3-year-old: an alternative anesthetic regimen to allay the concerns of the potential neurocognitive effects of general anesthesia. *J Med Cases.* 2016;7(3):109–113.

21. Suleman M, Edala T, Abraham E, Siddiqu S. Non-trigger anesthesia management in a patient with Leigh's syndrome presenting for dental rehabilitation. *Anesth Pain Med.* 2015;5(6):288–294.

22. Komatsu R, Turan AM, Orhan-Sungur M, et al. Remifentanil for general anaesthesia: a systematic review. *Anaesthesia.* 2007;62(12):1266–1280.