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Prevention of emergence agitation in seven children receiving low dose ketamine and propofol total intravenous anesthesia

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Abstract

Emergence agitation (EA) can be a distressing side effect of pediatric anesthesia. We observed no recurrence of EA after a low-dose ketamine infusion was added to propofol total intravenous anesthesia in a series of seven pediatric oncology patients repetitively anesthetized for radiation therapy. EA had been documented in all seven patients but did not recur in any of 122 subsequent anesthetics in which this technique was used. Based on these findings, we recommend the addition of low-dose ketamine to propofol infusions for total intravenous anesthesia in order to prevent EA in children with a history of EA.

Keywords

sedation; ketamine; propofol; emergence agitation; radiation therapy

Introduction

Propofol total intravenous anesthesia (TIVA) is an effective and well-tolerated anesthetic technique that allows smooth induction and rapid recovery, making it ideal for procedural sedation of children [1-4]. However, approximately 3.7% of children experience emergence agitation (EA) after propofol TIVA [5, 6]. This frequency is considerably less than that reported with sevoflurane (23.1%) [6], but effective prevention of EA has remained elusive. The efficacy of fentanyl [7, 8], clonidine [9], oxycodone [10], dexmedetomidine [11], midazolam [12], and ketamine [13, 14] for the prevention of EA after inhalation anesthesia has been investigated, but we are unaware of any studies of adjunct anesthetic agents for prevention of EA after propofol anesthesia. We describe a series of seven pediatric oncology patients repetitively anesthetized for radiation therapy with propofol TIVA who experienced

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documented EA. EA did not recur in any of the 122 subsequent anesthetics in these patients, in which a low-dose ketamine infusion was added to propofol TIVA.

Materials and Methods

Anesthetic Technique

Propofol TIVA is the standard regimen for radiation therapy in young children at our institution. For patients with a history of agitation on emergence from propofol or with a source of pain (e.g., recent postoperative status), the propofol-based regimen may be supplemented with benzodiazepines, opioids, and/or ketamine. For patients with allergy to propofol or a history of intolerance, a sedation regimen comprising combinations of opioid, benzodiazepine and/or ketamine is used. Propofol anesthesia is induced by administering successive boluses of 1 mg/kg until loss of consciousness occurs. Additional boluses are administered if the child responds to stimulation during positioning for radiation. A propofol infusion is then delivered at variable rates of 100 to 250 mcg/kg/min, via a Baxter AS50 auto-syringe infusion pump (Deerfield, Illinois).

When the ketamine-propofol technique was utilized, the two drugs were mixed together in a single syringe. The combination was administered as successive boluses until loss of consciousness was achieved, and was then infused throughout the procedure. Each bolus delivered a dose of 1 $mg \cdot kg^{-1}$ of propofol. The continuous infusion delivered 150-250 $mcg \cdot kg^{-1} min^{-1}$of propofol.

Data Collection

Institutional Review Board approval was obtained to retrospectively review the records of seven patients whose propofol TIVA for radiation therapy had been supplemented with a low-dose ketamine infusion over a period of 2 years at St. Jude Children's Research Hospital (St. Jude), a tertiary-care pediatric cancer research center.

We reviewed the recovery room nursing notes for all anesthetics in the 7 patients to identify the anesthetic session after which EA was first diagnosed and documented as inconsolable crying, thrashing behavior, or severe agitation. We then identified the anesthetic session when ketamine was first given and the number of sessions in which the ketamine-propofol regimen was used for each patient.

Results

A low-dose ketamine was added to the anesthetic regimens of patients known to have experienced EA in an attempt to prevent recurrence. In these 7 patients in whom EA had been documented in conjunction with previous anesthetics, ketamine and propofol were the only agents used in all subsequent anesthetics, for a total of 122 anesthetic sessions. Patient age, oncology diagnosis, and weight are summarized in Table 1.

The number of sessions in which the ketamine-propofol regimen was used for each patient is presented in Table 2. Table 3 summarizes the procedure duration, the dose and infusion rate of ketamine and propofol, and the dose ratio of ketamine to propofol for each patient.

The seven patients underwent a mean of 15.4 anesthetics (median, 12.5; range, 4-28) that included a low-dose ketamine infusion. The most frequent dose ratio of ketamine to propofol was 1:10 (range, 1:7 to 1:20). No EA was documented during recovery from ketamine-propofol anesthetics.

Discussion

EA after inhalation anesthesia has been well described [12, 15-17]. EA after propofol anesthesia has been less completely described [5, 6], and there are no reports on the prevention of EA following propofol TIVA in children. Our case series is the first to report the successful use of a low-dose ketamine infusion in preventing EA after propofol TIVA.

The patients in this series formed a fairly homogeneous group. All were aged between 2.5 and 4.5 years and three had a diagnosis of brain tumor. The central nervous system pathology in these patients and the pattern of repetitive daily anesthetics may have increased the likelihood of EA. However, it remains unclear whether either or both of these factors contribute significantly to the onset of EA.

Aside from their possible role in the etiology of EA, repetitive anesthetics for radiation therapy exacerbate the burden of EA. In this context, EA is highly disturbing to parents, patients, and recovery room personnel. Children are also at risk of physical harm during these episodes, and the need for additional supervision and medication often prolongs the recovery process [18, 19]. Therefore, it is important in our setting to minimize the incidence of EA.

Because the underlying cause of EA is unknown and a multitude of contributory factors, including preoperative anxiety, pain, and metabolic imbalances, have been implicated [9, 20], no single preventive therapy has been established. A number of agents, including fentanyl [7, 8], clonidine [9], oxycodone [10], dexmedetomidine [11], and midazolam [12], have been tried with variable success in preventing or treating EA.

Ketamine has recently been used to prevent EA associated with inhalation anesthetic agents [13, 14]. Kararmaz et al. found that 6 $mg \cdot kg^{-1}$ oral ketamine given to children 30 minutes before adenotonsillectomy under desflurane anesthesia reduced the incidence of EA from 56% to 18% [13]. Dalens et al. showed a reduced incidence of EA in children given 0.25 $mg \cdot kg^{-1}$ of intravenous ketamine at the end of MRI procedures under sevoflurane anesthesia (12% vs. 36% in the control group) [14]. Our case series adds to these findings that intravenous low-dose ketamine may be useful in preventing EA in children undergoing TIVA with propofol.

After we began using the ketamine-propofol technique, children who had previously experienced documented EA had no further episodes. In most patients (5 of 7), ketamine was added during the next anesthetic session after EA was documented. In two patients (cases 3 and 7), opioids were used in the next anesthetic session but were ineffective, and low-dose ketamine was started during the following session. In 5 of our 7 patients, EA was identified relatively early (by the fifth anesthetic session).

Our case series is not the first to report the use of ketamine in combination with propofol in children, but it is the first to examine the use of this combination to prevent EA after propofol TIVA. Several recent studies have examined low-dose ketamine with propofol for procedural sedation in children, mainly assessing the regimen's effect on hemodynamic stability [21-24]. These studies found that low-dose ketamine effectively offsets the cardiorespiratory depression caused by propofol while providing adequate sedation and analgesia. Willman et al. [25] demonstrated the safety and efficacy of administering the ketamine-propofol ("ketofol") combination from a single syringe to children and adults undergoing procedures in the emergency department.

Prospective randomized, controlled trials are needed to confirm the efficacy of ketamine in preventing EA and to compare it to other adjuvant agents. Further, we have used of this technique only in patients aged 5 years or less, and its effectiveness may differ in other age groups.

Low-dose ketamine infused in combination with propofol throughout the procedure appears to prevent EA in young children who undergo repetitive anesthesia for radiation therapy.

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Table 1

Patient age, oncology diagnosis, and weight

Case	Oncology diagnosis	Age[a] (y)	Weight[a] (kg)
1	Primitive neuro-ectodermal tumor	3.5	13.6
2	Rhabdomyosarcoma	3	15
3	Ependymoma	3	22
4	Neuroblastoma	3	12.5
5	Ependymoma	5	18.6
6a[b]	Neuroblastoma	3	15
6b[b]	Neuroblastoma	2.5	12.5
7	Wilms tumor	4.5	17

[a] Measured at time of first anesthetic for radiation therapy

[b] Patient 6 received two separate radiation therapy courses 8 months apart.

Table 2

Anesthetic sessions with ketamine

Case	Session EA diagnosed	Session ketamine introduced	Sessions with Ketamine-Propofol/ Total Sessions
1	3	4	28/31
2	3	4	26/29
3	5	7	26/32
4	0[a]	1	15/16
5	25	26	10/35
6a[b]	8	9	8/17
6b[b]	11	12	6/17
7	1	3	4/9

EA, emergence agitation

[a] Patient 4 was diagnosed with EA prior to their first radiation treatment.

[b] Patient 6 received two separate radiation therapy courses 8 months apart.

Table 3

Details of the ketamine-propofol regimen used for each patient

Case	Anesthetic duration (min)	Propofol dose (mg·kg^{-1})	Propofol infusion rate (mg·kg^{-1}min^{-1})	Ketamine dose(mg·kg^{-1})	Ketamine infusion rate (mcg·kg^{-1}min^{-1})	Ketamine-propofol dose ratio
1	34.79 (15-84)	10.67 (3.73-29.23)	0.32 (0.10-0.80)	1.28 (0.35-4.80)	29.3 (10.0-80.0)	1:10 (1:7-1:20)
2	43.15 (21-118)	11.24 (5.33-28.00)	0.27 (0.19-0.40)	1.12 (0.53-2.80)	27.2 (19.0-40.0)	1:10
3	42.88 (17-180)	12.31 (5.90-43.70)	0.32 (0.22-0.88)	1.71 (0.71-6.56)	44.0 (16.1-132.4)	1:7 (1:7-1:15)
4	46.44 (21-195)	14.13 (6.38-74.48)	0.30 (0.15-0.45)	1.28 (0.64-4.80)	29.3 (14.6-45.5)	1:10 (1:8-1:15)
5	31.00 (19-58)	8.47 (5.91-15.81)	0.28 (0.21-0.37)	0.85 (0.59-1.58)	27.9 (21.4-36.6)	1:10
6a[a]	39.00 (19-75)	11.82 (6.54-20.78)	0.32 (0.28-0.46)	1.18 (0.81-2.08)	31.6 (27.6-46.0)	1:10
6b[a]	18.50 (13-24)	7.32 (5.97-8.58)	0.41 (0.30-0.65)	0.73 (0.60-0.86)	41.3 (29.9-65.1)	1:10
7	28.75 (20-38)	8.53 (5.59-10.29)	0.30 (0.27-0.33)	0.85 (0.56-1.03)	29.8 (27.1-32.7)	1:10

All values are reported as median (range)

[a]Patient 6 received two separate radiation therapy courses 8 months apart.