Prevention of Emergence Agitation in Seven Children Receiving Low-dose Ketamine and Propofol Total Intravenous Anesthesia

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Emergence agitation (EA) can be a distressing side effect of pediatric anesthesia. We retrospectively reviewed the records of 7 pediatric oncology patients who received low-dose ketamine in conjunction with propofol for total intravenous anesthesia (TIVA) repeatedly for radiation therapy. EA signs were observed in all 7 patients in association with propofol TIVA but did not recur in any of 123 subsequent anesthetics sessions during which low-dose ketamine was added to propofol. Based on this experience, we suggest that low-dose ketamine added to propofol may be associated with prevention of EA in children with a history of EA with propofol TIVA.

Keywords: Emergence agitation, ketamine, propofol, radiation therapy, sedation.

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 lower than that reported with sevoflurane (23.1%)[6]; only 1 study found no difference in EA incidence after propofol and sevoflurane administration.[7] Effective prevention of EA has remained elusive. The efficacy of fentanyl,[8,9] clonidine,[10] oxycodone,[11] dexmedetomidine,[12] midazolam,[13] and ketamine[14,15] for EA prevention after inhalation anesthesia has been investigated, but we are unaware of any studies of adjunct anesthetic agents for EA prevention after propofol anesthesia.

In this retrospective study, we describe a series of 7 children with cancer who are repetitively anesthetized for radiation therapy with propofol TIVA who experienced signs of EA documented in the recovery records. When low-dose ketamine was added to the propofol regimen, EA did not recur in any of the 123 subsequent anesthetic sessions in these patients.

Materials and Methods

• *Anesthetic Technique.* The technique of choice for anesthesia for radiation therapy in our practice is propofol TIVA. For patients with a history of agitation on emergence from propofol or a source of pain (eg, recent postoperative status), a 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 in the radiation room 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 rates of 100-250 µg/kg/min via a Baxter Auto Syringe AS50 infusion pump (Deerfield, Illinois).[4]

When the ketamine-propofol technique was used in this series, the 2 drugs were mixed together in a single syringe. The combination was administered as successive boluses until loss of consciousness was achieved and then was infused throughout the procedure. Each bolus delivered a dose of 1 mg/kg of propofol, and the continuous infusion delivered 150-250 µg/kg/min of propofol. Most commonly, the ketamine-to-propofol ratio was 1:10, so the ketamine dose received in each induction bolus was 0.1 mg/kg and the ketamine dose infused during the procedure ranged from 15 to 25 µg/kg/min. In a few cases, propofol was used alone for bolus doses and ketamine was added to propofol for continuous infusion at the discretion of the clinician with no apparent change in effects for the patients. It is our usual practice to administer lidocaine before propofol in patients without central venous access; a peripheral vein is used for TIVA. TIVA emergence occurs in a standard postanesthesia recovery room.

• *Data Collection.* The anesthesia department identified patients who had experienced EA after propofol TIVA who later received the ketamine and propofol admixture for their subsequent recurring anesthetics.

Patient	Oncology diagnosis	Age[a] (y)	Weight[a] (kg)	Session sequence when EA observed	Session sequence when ketamine introduced	Total anesthetic sessions using ketamine-propofol (n = 123)	Total anesthetic sessions evaluated (n = 186)	EA recurrences with ketamine-propofol
1	Primitive neuroectodermal tumor	3.5	13.6	3	4	28	31	0
2	Rhabdomyosar-coma	3.0	15.0	3	4	26	29	0
3	Ependymoma	3.0	22.0	5	7	25	32	0
4	Neuroblastoma	3.0	12.5	0[c]	1	16	16	0
5	Ependymoma	5.0	18.6	25	26	10	35	0
6a[b]	Neuroblastoma	3.0	15.4	8	9	8	17	0
6b[b]	Neuroblastoma	2.5	12.5	11	12	6	17	0
7	Wilms tumor	4.5	17.0	1	3	4	9	0
	Mean	3.4	15.8	7	8.25	15.4	23.3	0

Table 1. Characteristics of Patients with Emergence Agitation (EA) After Anesthetics for Radiation Therapy
[a] At the time of first anesthetic with ketamine for radiation therapy.
[b] Patient 6 received 2 separate radiation therapy courses 8 months apart.
[c] EA was diagnosed in patient 4 before the first radiation treatment.

Institutional review board approval was obtained to retrospectively review the records of these 7 patients who received radiation therapy with ketamine and propofol over a 2-year period at St. Jude Children's Research Hospital (St. Jude), a tertiary-care pediatric cancer research center in Memphis, Tennessee.

We reviewed the recovery room nursing notes regarding all anesthetics to identify the anesthetic session after which signs of EA were first observed in the 7 patients. We were looking for documentation of inconsolable crying, thrashing behavior, or severe agitation. We then identified the anesthetic session during which ketamine first was given and the total number of sessions during which the ketamine-propofol regimen was used for each patient, again reviewing recovery room nursing notes for documentation of the EA signs.

Results

In an attempt to prevent recurrence, low-dose ketamine was added to the anesthetic regimens of patients known to have experienced EA during a previous anesthetic session. In all but 2 cases, the ketamine-propofol combination was used for the next anesthetic session and all subsequent sessions. In 2 cases, another agent (fentanyl or midazolam) was used first to attempt to control recurrence of EA but failed, and the ketamine-propofol combination was used for all subsequent sessions. The ketamine-propofol combination was used for a total of 123 anesthetic sessions. Table 1 summarizes the patient demographics and the number and sequence of sessions during which EA was observed and the ketamine-propofol combination was used. Table 2 summarizes the mean and range data for anesthetic duration, doses of propofol and ketamine, and the dose ratio of ketamine to propofol used for each patient.

All patients reviewed were younger than 5 years old and had solid tumors (3 brain tumors) for which they were receiving radiation therapy under anesthesia (average of 23.3 sessions per patient). In 5 of 7 patients, EA signs were observed on or before the fifth session of their radiation therapy regimens. The 7 patients underwent an average of 15.4 subsequent anesthetics (median, 12.5; range, 4-28) that included the low-dose ketamine infusion. The most common dose ratio of ketamine to propofol was 1:10 (range 1:7-1:20). No signs consistent with EA were documented during recovery from ketamine-propofol anesthetics in the study group. Repeated use of the anesthetic combination with good recovery suggests this anesthetic technique may be associated with control of EA in the patients studied.

Discussion

EA after inhalation anesthesia has been well described.[13,16-18] EA after propofol anesthesia has been less completely described,[5,6] and there are no reports on the prevention of EA recurrence after repetitive propofol TIVA in children. Our case series is the first to report the association of a low-dose ketamine infusion with the

Patient	Anesthetic duration (min)	Propofol (mg/kg)	Propofol (µg/kg/min)	Ketamine (mg/kg)	Ketamine (µg/kg/min)	Ketamine-propofol ratio
1	34.79 (15-84)	10.67 (3.73-29.23)	320 (100-800)	1.08 (0.35-2.92)	29.3 (10.0-80.0)	1:10 (1:7-1:20)
2	43.15 (21-118)	11.24 (5.33-28.00)	270 (190-400)	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)	320 (220-880)	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)	300 (150-450)	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)	280 (210-370)	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)	320 (280-460)	1.18 (0.65-2.08)	31.6 (27.6-46.0)	1:10
6b[a]	18.50 (13-24)	7.32 (5.97-8.58)	410 (300-650)	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)	300 (270-330)	0.85 (0.56-1.03)	29.8 (27.1-32.7)	1:10

Table 2. Duration of Anesthetic and Total Propofol and Ketamine Doses (Mean and Range) and Ratios
[a] Patient 6 received 2 separate radiation therapy courses 8 months apart.

prevention of EA recurrence after propofol TIVA.

The patients in this series formed a fairly homogeneous group. All were between 2.5 and 5 years old and 3 patients had brain tumors. 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 substantially to EA onset.

Aside from their possible role in EA etiology, repetitive anesthetics for radiation therapy exacerbate the EA burden. 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.[19,20] Consequently, it is important in our setting to minimize EA incidence.

Because the underlying cause of EA is unknown and a multitude of contributory factors including preoperative anxiety, pain, and metabolic imbalance have been implicated,[10,21] no single preventive therapy has been established. A number of agents including fentanyl,[8,9] clonidine,[10] oxycodone,[11] dexmedetomidine,[12] and midazolam[13] have been tried with variable success in preventing or treating EA.

Ketamine has been reported to prevent EA associated with inhalation anesthetic agents.[14,15] Kararmaz et al found that 6 mg/kg oral ketamine given to children 30 minutes before adenotonsillectomy under desflurane anesthesia reduced EA incidence from 56% to 18%.[14] Dalens et al showed a reduced incidence of EA in children given 0.25 mg/kg of ketamine administered intravenously at the end of MRI procedures while under sevoflurane anesthesia (12% vs 36% in the control group).[15] Our case series adds to these findings; we suggest that low-dose ketamine administered intravenously may be associated with prevention of recurrent EA in children undergoing repetitive TIVA with propofol.

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 studies have examined use of low-dose ketamine with propofol for procedural sedation in children, mainly assessing the regimen's effect on hemodynamic stability.[22-25] These studies found that low-dose ketamine effectively offsets the cardiorespiratory depression caused by propofol while providing adequate sedation and analgesia. Willman et al[26] demonstrated the safety and efficacy of administering the 1:1 ketamine-propofol ("ketofol") combination from a single syringe to children and adults undergoing procedures in the emergency department. None of these studies examined a combination as low as the 1:10 ketamine-to-propofol mixture used in our series.

Limitations

Our study has limitations inherent in retrospective case studies. We were unable to apply a standard definition for EA or use an existing scoring tool because of the retrospective nature of the study. Evaluation by an independent observer using a valid and reliable instrument to measure EA is possible in prospective studies.[27] However, at our institution, staff and families are well

informed about patients who have EA signs, and all patients undergoing radiation therapy who received the propofol-ketamine combination during the defined time were included in our review.

Ketamine dosing was standardized as much as possible concurrent with clinical use; a low 1:10 ratio appeared to be effective in our case series. The total doses of propofol administered per weight (mg/kg) vary from case to case; nevertheless, when examining the total dose expressed as a matter of time (μg/kg/min), one can note that variations in dosage per time are not wide and reflect little variability in the depth of anesthesia across cases. The sedation duration and depth was defined by the patient's situation (primarily to prevent movement for the entire radiation therapy session) and not by a policy or prospective research protocol.

The review of recovery times and other postanesthesia care unit measures were not aims of our study; our local practice allows all patients with an EA history to remain asleep as long as needed to help prevent an agitated arousal. In addition, because we used this technique only in patients 5 years old or younger with solid tumors, its effectiveness may differ in other pediatric subsets.

Conclusion

Low-dose ketamine infused in combination with propofol TIVA appears to be associated with prevention of EA recurrence in young children who undergo repetitive anesthesia for radiation therapy. A clear determination of cause and effect cannot be made on the basis of our retrospective analysis; prospective randomized controlled trials are needed to confirm the efficacy of ketamine in preventing EA and compare it to other adjuvant agents.

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