RESEARCH ARTICLE

The Incidence and Nature of Allergic and Anaphylactic Reactions During Pediatric Procedural Sedation: A Report From the Pediatric Sedation Research Consortium

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ABSTRACT

BACKGROUND AND OBJECTIVES: Anaphylaxis is rare but life-threatening. Its incidence during pediatric procedural sedation outside of the operating room is unknown. We used data from the Pediatric Sedation Research Consortium (PSRC) to determine the incidence and nature of allergic and anaphylactic reactions in this practice.

METHODS: A retrospective observational study of prospectively collected information in the PSRC's multicenter database was performed. Cases of allergic reaction were identified. Because anaphylaxis is not a listed complication in the PSRC database, all cases for which allergic reaction was noted were reviewed for the occurrence of other complications or interventions that would suggest at least 2 organ system derangements consistent with anaphylaxis as well as for practitioner commentary stating the occurrence of anaphylaxis. Descriptive analyses of demographic information and summary statistics were performed, and multiple logistic regression analysis was used to evaluate associations between the occurrence of allergic reactions and medications.

RESULTS: During the study period, 227 833 cases were entered into the PSRC database. There were 54 cases of allergic reaction (incidence 1:4219); 6 were consistent with anaphylaxis (incidence 1:37 972). A significant association between the development of allergic reaction and 4 sedative and/or analgesic medications was noted: midazolam (odds ratio [OR] 2.2; confidence interval [CI] 1.2–3.9), ketamine (OR 3.8; CI 2.1–7.1), methohexital (OR 48.8; CI 14.9–159.9), and morphine (OR 4.4; CI 1.04–18.2). There were no mortalities.

CONCLUSIONS: Allergic reactions and anaphylaxis during pediatric procedural sedation are rare. In this study, the development of allergic reactions was significantly associated with the use of midazolam, ketamine, methohexital, and morphine.

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Pediatric procedural sedation (PPS) is often used to facilitate diagnostic and therapeutic interventions in children. Multiple different specialists provide PPS, including pediatricians, anesthesiologists, intensivists, and emergency medicine physicians, and a variety of pharmacologic agents are employed. Inherent to this practice is the risk for the development of allergic and anaphylactic reactions in patients. Anaphylaxis is a serious, systemic hypersensitivity reaction, usually of rapid onset, that may result in mortality.[1] Although the incidence of anaphylaxis in adults during general anesthesia is estimated to be 1:10 000 to 1:20 000 cases,[2] the incidence of anaphylaxis or allergic reactions during PPS is unknown but is unlikely to be equivalent. We used data from the Pediatric Sedation Research Consortium (PSRC) to evaluate the nature and incidence of allergic and anaphylactic reactions during PPS, the mortality rate associated with allergic and anaphylactic reactions during PPS, and the relationship between the development of allergic and anaphylactic reactions and the use of sedatives, analgesics, local anesthetics, and radiographic contrast material.

METHODS

A retrospective, observational study of prospectively obtained information collected in the PSRC's multicenter database was performed. The PSRC is a collaborative group of sedation providers who are dedicated to the provision of optimal procedural sedation care in children. The PSRC maintains a database to collect data on PPS as practiced by its members. PSRC members provide PPS in a variety of locations, including free-standing children's hospitals, children's hospitals within academic medical centers, community hospitals, free-standing imaging centers, and dental offices. Institutional review board approval for participation in the database is required of all individual institutions, as is the use of individual site primary investigators who are responsible for overseeing standardized data entry and quality. The data collection methodology has been described in a report of the first 30 000 sedation cases from the PSRC database[3] as well as in subsequent publications.[4,5]

A standardized, Web-based data collection tool with which a secure site data system is used and maintained by the Dartmouth Bioinformatics Group was used for data collection and storage. The data collected included information on patient demographics, diagnoses, procedures performed, medications administered, adverse events, and interventions. Free-text commentary detailing additional case information could also be entered at the discretion of the site sedation provider. Only deidentified data were collected. Allergic reaction is 1 of the predefined adverse events listed in the database and is defined as urticaria, rash, breathing difficulty, angioedema and/or anaphylaxis temporally related to the delivery of sedation medication. This definition was readily accessible to data entry personnel via pop-up text. Anaphylaxis is not specifically listed as a predefined adverse event in the database.

The data collection period evaluated was November 10, 2011, to January 6, 2017 (62 months). All cases for which the adverse event of allergic reaction was selected had their database information reviewed. Because data are deidentified, individual patient medical records could not be reviewed, and it could not be determined if a single patient was involved in >1 episode of allergic reaction. To determine the occurrence of anaphylaxis, 2 of the authors (J.H.H. and K.P.) reviewed the case data for all patients who experienced an allergic reaction as an adverse event, with the intent being to make a consensus determination as to whether the episode involved a derangement of ≥ 2 organ systems.[6] Predefined adverse events in the database that were considered to be supportive of (but not diagnostic of) an episode of anaphylaxis included airway obstruction; cardiac arrest; death; emergency anesthesia, code team, or rapid response team notification; a procedure not being completed because of sedation-related problems; a requirement for emergent airway intervention; stridor; an unplanned admission to the hospital or increased level of care; vomiting (nongastrointestinal procedure); wheezing; or other (specified). The administration of epinephrine was also considered to be supportive of an episode of anaphylaxis. In addition, free-text comments could be included by the practitioner in the case record such that anaphylaxis could be identified when noted.

Standard demographic information for all cases was obtained, including age, weight, sex, American Society of Anesthesiologists physical status classification, primary reason for procedure, coexisting medical problems, procedure, location, and provider. The incidence of allergic reaction and the incidence of anaphylaxis was determined, as was the mortality rate.

The association between the occurrence of allergic reaction and the use of pharmacologic agents, including sedatives, analgesics, and local anesthetics, was evaluated by using multiple logistic regression analysis.

Radiographic contrast material is another important cause of anaphylaxis. Although the use of radiographic contrast material is not recorded in the database, patients with allergic and anaphylactic reactions were evaluated for whether they underwent either a computed tomography (CT) or MRI scan. Because the timing of the allergic or anaphylactic reaction is noted in the database as occurring before, during, or after the procedure, radiographic contrast material was not considered to be a potential cause of allergic or anaphylactic reaction when the reaction occurred before the procedure (and thus before the injection of contrast material).

Statistical analysis was performed by using Stata IC version 13.1 (Stata Corp, College Station, TX). Demographic information is expressed as a mean $\pm$ SD. Incidence rates are expressed as events per 10 000 cases. Multiple logistic regression analysis was performed to evaluate for associations between sedative and/or analgesic agents and allergic reactions while controlling for the use of multiple agents. Odds ratios (ORs) with confidence intervals (CIs) were determined for those agents for which a significant association was found. $P \leq .05$ was considered to be statistically significant.

RESULTS

Fifty-four PSRC member centers (see below) submitted 227 833 cases of PPS over the 62-month evaluation period. In 54 of these cases, the adverse event allergic reaction was recorded. After independent author review, there was agreement that in 45 of the cases, anaphylaxis did not occur, and 3 of the cases were consistent with anaphylaxis. In 2 cases, the presence of anaphylaxis could not be determined on the basis of available information. In 4 cases, the authors disagreed on whether anaphylaxis had occurred. The authors subsequently jointly reviewed the 4 cases for which there was disagreement and determined that 3 of the cases were consistent with anaphylaxis. As a result, 48 cases were considered to be limited to an allergic reaction (including the 2 cases for which the occurrence of anaphylaxis could not be determined), whereas 6 cases were considered to be consistent with anaphylactic reactions. The total number of allergic reaction cases were reported by 25 centers. Cases that were considered to be consistent with anaphylaxis were reported by 3 sites, with 1 site reporting 4 of the 6 cases.

Based on 54 cases of allergic reaction, the incidence of allergic reactions in our data set is 1:4219. Likewise, based on 6 cases of anaphylaxis, the incidence of anaphylactic reactions in our data set is 1:37 972. No mortality occurred during this study period.

Demographic characteristics for all cases are presented in Table 1. Patient characteristics were similar for those experiencing nonanaphylactic reactions and those experiencing anaphylaxis. All patients who experienced anaphylaxis were scheduled for MRI, whereas those patients experiencing nonanaphylactic allergic reactions or who had no reaction underwent a variety of procedures. Twenty-seven percent of all the patients underwent >1 procedure (such as bone marrow biopsy and/or aspiration and lumbar puncture in oncology patients).

The symptoms of nonanaphylactic allergic reactions (as determined from the database list of adverse events and providers' free-text commentary) included respiratory symptoms in 31% of cases, dermatologic symptoms in 17% of cases, and gastrointestinal symptoms in 2% of cases. However, no symptoms were documented in the database for 50% of the cases.

The medications used in all cases are shown in Table 2. In cases in which allergic reactions occurred, 61% received ≥ 2 sedative and/or analgesic medications (excluding intravenous [IV] lidocaine and topical numbing agents). Diphenhydramine was administered in 48% of these cases; 92% of these procedures were completed. With regard to the potential role of radiographic contrast material in the development of allergic reaction, 21 patients received an MRI scan, and 1 patient received a CT scan. The timing of the allergic reaction was noted to be before the procedure in 5 cases, excluding radiographic contrast material as an etiologic agent. In the other 17 cases, the allergic reaction occurred during or after the procedure, but the use of radiographic contrast material was not recorded in these cases.

The medications used in cases in which anaphylaxis occurred are also shown in Table 2. Specifics on each case obtained from the database are as follows:

Case 1: A 3-year-old boy with an egg allergy had tolerated propofol sedation the previous day. He received only propofol for sedation. During the procedure, the patient developed a cough, secretions, and oxygen desaturation, and the procedure was aborted. The patient subsequently developed pruritus without urticaria, stertorous breathing, and wheezing. The patient was treated with epinephrine, diphenhydramine, and solumedrol. Airway suction and repositioning and nasopharyngeal airway placement were performed, and supplemental oxygen was administered. The patient was admitted to the PICU.

Case 2: A 16-year-old girl with severe food allergies (but not to soy or egg) and previous episodes of anaphylaxis that required tracheal intubation. She had previously tolerated propofol sedation. She received propofol with IV lidocaine and topical numbing agents. During the procedure, she developed anaphylaxis with severe tongue swelling, and the procedure was aborted. She was treated with epinephrine (both intramuscular [twice] and IV), diphenhydramine, and solumedrol as well as supplemental oxygen. The patient was admitted to the PICU.

Case 3: A 3-year-old boy with an egg allergy was seen. Because of this allergy, methohexital was used for sedation along with topical numbing agents. The patient developed secretions, stridor, and wheezing before the procedure, and the procedure was aborted. The patient received racemic epinephrine, diphenhydramine, solumedrol, nebulized albuterol, and ranitidine. He also received airway suction and repositioning, mask continuous positive airway pressure (CPAP), jaw thrust, and supplemental oxygen, and a nasopharyngeal airway was placed. The patient was transferred to the emergency department for monitoring and was discharged later that day.

Case 4: A 4-year-old boy received a topical numbing agent and a bolus of propofol when he developed secretions and wheezing before the procedure, and the procedure was aborted. The patient received racemic epinephrine, diphenhydramine, solumedrol, nebulized albuterol, and ranitidine. He also received airway suction and repositioning, mask CPAP, jaw thrust, and supplemental oxygen.

Case 5: An 8-year-old boy received propofol with IV lidocaine and IV fentanyl. He developed a cough and airway obstruction, which were managed with mask CPAP, bag-valve-mask ventilation, and jaw thrust. The procedure was attempted but was aborted after continued symptoms along with the development of secretions, wheezing, and urticaria. Airway suction was performed in addition to the previously described therapies. Medical therapies for anaphylaxis were not noted.

Case 6: A 3-year-old girl received a propofol bolus and developed a cough. No other symptoms are documented, but it was noted that the patient had an

TABLE 1 Demographics

	Allergic (n = 48)	Anaphylaxis (n = 6)	All Other (n = 227 779)
Age, y, mean ± SD	7.6 ± 4.9	6.2 ± 5.2	6.3 ± 5.0
Wt, kg, mean ± SD	31.0 ± 18.8	27.6 ± 18.8	27.0 ± 20.3
Girls, % (n)	45.8 (22)	50 (3)	44.7 (101 880)
ASA PS, % (n)			
1	27.1 (13)	—	20.1 (45 755)
2	50 (24)	67 (4)	59.9 (136 513)
3	16.7 (8)	33 (2)	16.7 (38 161)
4	—	—	0.3 (762)
1 emergent	6.2 (3)	—	0.9 (2025)
2 emergent	—	—	0.2 (449)
3 emergent	—	—	0.05 (107)
4 emergent	—	—	0.01 (18)
No data available	—	—	1.8 (3989)
Principle diagnosis, % (n)			
Neurologic (other than seizure)	18.8 (9)	50 (3)	22 (50 108)
Hematology and/or oncology (other than leukemia)	14.5 (7)	16.7 (1)	12.7 (29 009)
Orthopedic	14.5 (7)	—	4.8 (11 038)
Gastrointestinal	12.5 (6)	—	10.1 (23 146)
Status posttrauma	—	33.3 (2)	0.9 (1959)
Infection	6.3 (3)	—	4.7 (10 622)
Metabolic and/or genetic	6.3 (3)	—	1.4 (3252)
Renal	6.3 (3)	—	4.9 (11 193)
Dermatologic	4.1 (2)	—	0.7 (1601)
Seizure disorder	4.1 (2)	—	6.9 (15 665)
Craniofacial	2.1 (1)	—	0.8 (1880)
Hearing deficiency	2.1 (1)	—	2.9 (6725)
Leukemia	2.1 (1)	—	13 (29 636)
Lower respiratory	2.1 (1)	—	0.8 (1889)
Surgical wound management	2.1 (1)	—	0.7 (1548)
Burn injury	—	—	0.5 (1135)
Cardiovascular	—	—	1.4 (3159)
Congenital anomaly	—	—	0.6 (1317)
Dental	—	—	1.6 (3552)
Developmental delay	—	—	2.2 (4976)
Immune compromise	—	—	0.1 (197)
Liver disease	—	—	0.4 (846)
Prematurity	—	—	0.1 (112)
Rheumatology	—	—	0.7 (1695)
Status posttransplant	—	—	0.3 (705)
Unknown growth and/or mass	—	—	1.7 (3846)
Upper respiratory	—	—	0.2 (457)
Foreign body	—	—	0.1 (181)
Psychiatric	—	—	0.1 (231)
Other	2.1 (1)	—	—
Procedure, % (n)			
MRI	37.6 (18)	100 (6)	40.9 (93 136)

TABLE 1 Continued

	Allergic (n = 48)	Anaphylaxis (n = 6)	All Other (n = 227 779)
Fracture reduction	10.4 (5)	—	1.8 (3984)
Upper endoscopy	10.4 (5)	—	7.4 (16 922)
Botox injection	6.3 (3)	—	1.7 (3815)
Gastrointestinal (other than endoscopy)	4.1 (2)	—	1.8 (4093)
PICC	4.1 (2)	—	2.9 (6686)
VCUG	4.1 (2)	—	2.0 (4543)
Other	4.1 (2)	—	8.4 (19 026)
ABR	2.1 (1)	—	2.8 (6412)
CT	2.1 (1)	—	5.0 (11 438)
Echocardiogram	2.1 (1)	—	1.0 (2225)
LP diagnostic, MRI	2.1 (1)	—	—
LP diagnostic, other painful procedure	2.1 (1)	—	—
LP and chemotherapy	2.1 (1)	—	13.9 (31 672)
Minor surgical	2.1 (1)	—	2.5 (5610)
Other painful procedure	2.1 (1)	—	4.5 (10 193)
Renal and/or bone scan	2.1 (1)	—	1.5 (3469)
LP diagnostic or therapeutic	—	—	22.7 (51 615)
Colonoscopy	—	—	21.6 (49 170)
Bone marrow aspiration and/or biopsy	—	—	4.6 (10 420)
Dental	—	—	1.6 (3583)
Provider, % (n)			
Intensivist	47.9 (23)	66.6 (4)	57.5 (130 983)
Hospitalist	16.7 (8)	16.7 (1)	7.9 (18 073)
Pediatric emergency medicine	18.8 (9)	—	18.1 (41 299)
Pediatrician (subspecialist)	—	16.7 (1)	1.0 (2197)
Pediatric anesthesiologist	12.5 (6)	—	9.6 (21 967)
Advanced practice nurse and/or physician assistant	4.1 (2)	—	3.0 (6767)
Anesthesiologist	—	—	0.1 (219)
Emergency medicine	—	—	0.2 (487)
Fellow (any specialty)	—	—	0.2 (507)
Radiologist	—	—	0.1 (164)
Registered nurse	—	—	0.1 (149)
Dentist	—	—	1.1 (2526)
Other	—	—	1.1 (2441)

ABR, auditory brainstem response; ASA PS, American Society of Anesthesiologists physical status; LP, lumbar puncture; PICC, peripherally inserted central catheter; VCUG, voiding cystourethrogram; —, not applicable.

> "anaphylactic reaction, likely to propofol." The procedure was aborted. The patient received supplemental oxygen, racemic epinephrine, albuterol nebulized twice, diphenhydramine, and solumedrol.

The development of anaphylaxis occurred before the start of the MRI in 4 of the cases, excluding gadolinium exposure as a cause of anaphylaxis. In the other 2 cases, anaphylaxis occurred during or after the procedure, but the use of gadolinium in these cases is unknown.

Multiple logistic regression analysis revealed a significant association between the development of an allergic reaction and 4 sedative and/or analgesic medications: midazolam (OR 2.2; CI 1.2–3.9), ketamine (OR 3.8; CI 2.1–7.1), methohexital (OR 48.8; CI 14.9–159.9), and morphine (OR 4.4; CI 1.04–18.2). This correlates to the following risk rate for developing an allergic reaction in association with each specific agent: midazolam, 1:2035; ketamine, 1:1147; methohexital, 1:131; and morphine, 1:601. The small number of anaphylaxis cases precludes a meaningful statistical analysis of possible associations with specific medications.

DISCUSSION

Anaphylactic reactions are rare but life-threatening events that may occur in a

TABLE 2 Medications

	Allergic (n = 48), % (n)	Anaphylaxis (n = 6), % (n)	All Other (n = 227 779), % (n)
Propofol	64.6 (31)	83.3 (5)	83.3 (189 777)
Midazolam	43.8 (21)	—	18.8 (42 705)
Topical numbing agent	39.6 (19)	50 (3)	22.8 (51 990)
Ketamine	33.3 (16)	—	8.1 (18 333)
Fentanyl	22.9 (11)	16.6 (1)	19.7 (44 942)
Lidocaine (IV)	22.9 (11)	16.6 (1)	—
Dexmedetomidine	8.3 (4)	—	5.9 (13 453)
Methohexital	4.2 (2)	16.6 (1)	0.2 (390)
Pentobarbital	4.2 (2)	—	1.3 (3057)
Morphine	4.2 (2)	—	0.5 (1200)
Chloral hydrate	2.1 (1)	—	0.5 (1242)
Hydromorphone	—	—	19.6 (44 942)
Nitrous oxide	—	—	4.6 (10 537)

—, not applicable.

variety of clinical situations. During general anesthesia in adults, the incidence of anaphylaxis is estimated to be 1:10 000 to 1:20 000 cases, with perioperative anaphylaxis mortality estimates ranging from 1.4% to 6% and an additional 2% of patients suffering neurologic injury.[2] This morbidity and mortality rate is higher than that seen for anaphylaxis in general, and it may be due to the more rapid exposure to inciting agents with the use of IV medications, delayed recognition and treatment (due to the patients' inability to communicate symptoms and the covering of skin with surgical drapes), and increased vulnerability due to surgically related physiologic changes.[2] However, it is likely that the incidence of these events is lower for children than for adults.[7] In a multicenter study from 1993, Murat[8] evaluated 162 551 children undergoing general anesthesia and determined that the incidence of anaphylactic reactions was 1:7741. However, 76% of these reactions were deemed to be secondary to latex exposure, which currently is an uncommon etiology for anaphylaxis in the operating room given the emphasis on a latex-free environment over the past 2 decades. There are no other published rates for the incidence of anaphylaxis during general anesthesia for children.

The incidence of anaphylactic reactions during PPS for procedures outside the operating room is unknown. Although sedation and anesthesia occur on a continuum, it is unlikely that the incidence of anaphylaxis during both is equivalent. During general anesthesia, the majority of anaphylactic events are attributed to neuromuscular blocking agents and antibiotics,[2] which are medications that are not commonly administered during PPS. Induction agents for general anesthesia, such as barbiturates, benzodiazepines, propofol, etomidate, and ketamine, are commonly used for PPS but account for no more than 2% of anaphylaxis episodes related to general anesthesia in adults.[2] Recently, Spera et al[9] evaluated the Society for Ambulatory Anesthesia Clinical Outcomes Registry for deep sedation and/or general anesthesia for outpatient pediatric dentistry. Of the 7041 cases in the registry, no episodes of anaphylaxis were recorded. Given the likely low incidence of anaphylaxis in this situation, it is possible that this registry contained too few cases for this rare event to be observed.

The PSRC database is a large, multicenter project in which a large number of sedation events are enrolled such that infrequent events are likely to be captured. We found that in the practice of the PSRC, the incidence of allergic reactions during PPS was 1:4219, whereas the incidence of anaphylactic reactions was 1:37 972 during PPS. No mortality was noted. To our knowledge, this is the first report of these incidences. As anticipated, our reported incidence of anaphylaxis is less than that seen during general anesthesia in adults, as previously discussed.

We found an association between the development of an allergic reaction and the use of midazolam, ketamine, methohexital, and morphine. During general anesthesia in adults, barbiturates, such as methohexital, are generally noted to be the induction agent that is responsible for anaphylactic reactions, whereas midazolam, ketamine, and morphine are not typically associated with anaphylaxis.[2] Our findings of a risk rate for allergic reaction of 1 per 131 cases when methohexital was used, with less dramatic risk rates for midazolam, ketamine, and morphine, are consistent with the adult experience during general anesthesia. It is interesting to note, however, that an association between the development of allergic reactions and the use of pentobarbital, a commonly used barbiturate in PPS, was not found in this study.

Propofol is a commonly used agent for PPS, and practitioners remain concerned about the role of propofol in the development of allergic and anaphylactic reactions. Although an association between egg, soy, and peanut allergies and the development of allergic or anaphylactic reactions with the use of propofol is no longer supported, allergies to propofol itself exist.[10] In this study, when propofol use is analyzed separately, a significant association with

allergic reaction is present, but this association is no longer significant when controlling for other drugs that are used concomitantly. This likely reflects the common use of propofol for PPS in the PSRC and the relatively small number of allergic reactions. Furthermore, the small number of anaphylaxis cases precludes a meaningful statistical analysis of an association between anaphylaxis cases and propofol administration.

Radiographic contrast material is another important causative agent for allergic and anaphylactic reactions. The overall frequency of adverse events is 5% to 8%, but life-threatening reactions occur in <0.1% of cases when conventional high-osmolality agents are used, with a likely lower incidence seen when lower-osmolality agents are used.[2] Although radiographic contrast material may have potentially been administered in several of the cases in which allergic and anaphylactic reactions occurred, the database does not contain enough detail to determine the use and timing of radiographic contrast material to allow for an accurate analysis.

In previous reports from the PSRC, researchers have outlined the limitations of our database.[3–5] As noted previously, anaphylaxis is not a defined complication in the database, raising the possibility that we may have incorrectly identified such cases. However, our methodology of independent and collaborative author review of all cases in which allergic reaction was noted should have allowed for an effective identification of anaphylaxis cases. In 2 of the cases, the occurrence of an anaphylactic reaction could not be determined because of limited information in the database, and therefore, they were considered to be allergic reaction only. If either of these cases did involve anaphylaxis, then this would impact our reported incidence rate. Ultimately, an evaluation of serum tryptase levels at the time of a suspected allergic or anaphylactic reaction would provide certainty in the diagnosis, but such information is not recorded in the PSRC database. As noted previously, we can make no assessment on the potential association of radiographic contrast material with the development of allergic and anaphylactic reactions because of limitations in the database. This should be an area of further research. Also of interest is that food allergies were noted in half of the anaphylaxis cases, but limitations in the database prevent further analysis because the presence of food allergies is not a standard query. This also should be an area of further research. We also note that 4 of the 6 cases of anaphylaxis occurred in 1 PSRC center, raising the possibility of a center effect or potential selection bias (in that this center may have overdiagnosed anaphylaxis or been better than other centers in diagnosing and documenting cases of anaphylaxis). Finally, we recognize that the PSRC may have better-performing systems and that outcomes may differ in other centers that provide PPS.

CONCLUSIONS

Allergic reactions and anaphylaxis are rare during PPS, and the incidence of anaphylaxis is less than that that reported in adults undergoing general anesthesia. We found an association between allergic reaction during PPS and the use of midazolam, ketamine, methohexital, and morphine. Future researchers should focus on the role of radiographic contrast material and food allergies in the development of allergic and anaphylactic reactions during PPS.

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