Practice Patterns and Adverse Events of Nitrous Oxide Sedation and Analgesia: A Report from the Pediatric Sedation Research Consortium

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Objectives To describe practice patterns and adverse events associated with nitrous oxide (N_2O) administration as the primary sedative outside the operating room in varied settings by a diverse range of providers, and to identify patient and sedation characteristics associated with adverse events.

Study design Data prospectively collected by the Pediatric Sedation Research Consortium, which is comprised of 40 children's and general/community hospitals, was retrospectively analyzed for children who received N_2O as the primary sedative. Descriptive measures of patient and sedation characteristics and adverse events were reported. A multivariable regression model was used to assess potential associations between patient and sedation characteristics and adverse events.

Results A total of 1634 N_2O administrations were identified. The majority was performed in sedation units, and most by advanced practice nurses or physician assistants. The most common adjunct medication was midazolam. There was a low prevalence of adverse events (6.5%), with vomiting as the most common (2.4%) and only 3 (0.2%) serious adverse events reported. The odds of vomiting increased when concomitant opioids were administered (OR 2.89, 95% CI 1.14, 7.32) and when nil per os (NPO) clear fluids <2 hours (OR 4.16, 95% CI 1.61, 10.76). NPO full meal <6 hours did not change the odds of vomiting (OR 1.42, 95% CI 0.57, 3.57). There were no aspiration events.

Conclusions There was a very low prevalence of serious adverse events during N_2O administration in children outside of the operating room and by nonanesthesiologists. The odds of vomiting increased when concomitant opioids were administered and NPO clear fluids <2 hours. *(J Pediatr 2016;169:260-5)*.

Nitrous oxide (N_2O) is a colorless, odorless, gas with anxiolytic, analgesic, and amnestic properties, and a longstanding history of use by anesthesiologists and dentists.[1-4] Given its favorable sedative characteristics and impressive record of safety, the use of N_2O for facilitating painful and/or distressing procedures in children has been adopted for use by other providers in settings outside of the operating room, in addition to dental practices. Nurse practitioners, hospitalists, emergency medicine physicians, and intensivists administer N_2O in their respective settings and in the context of a sedation service for a wide variety of procedures in the pediatric population.[1,5-15]

The practice patterns and adverse events associated with N_2O administration performed by this varied population of practitioners in these settings have not been well described. Most descriptions of N_2O administration to date have been limited to reports from individual centers with a specific scope of practice. It is unclear if their experiences and reported adverse event profiles are generalizable to a broader and more diverse population of providers.[1,7-14]

Our aim was to describe the practice patterns of N_2O sedation and analgesia in children outside of the operating room among a consortium of pediatric sedation services. We also aimed to describe the adverse events associated with N_2O administration in these contexts and to identify any patient and sedation characteristics associated with adverse events.

Methods

We retrospectively analyzed consecutive pediatric N_2O administrations from the Pediatric Sedation Research Consortium (PSRC) database between November 2011 and July 2014. Data was prospectively collected, and each administration corresponded to a unique patient.

The data collection methodology of the PSRC has been detailed in a report of its first 30 000 sedations, and in subsequent publications involving up to 140 000 sedation encounters.[11,16-19]

ASA	American Society of Anesthesiologists
ED	Emergency department
IV	Intravenous
N_2O	Nitrous oxide
NPO	Nil per os
PSRC	Pediatric Sedation Research Consortium

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During the study period, the PSRC was comprised of 40 self-selected locations, including children's hospitals and general/community hospitals. Participating institutions all obtained institutional review board approval and agreed to a standardized methodology for consecutive data collection and quality oversight. Data collection was performed using a Web-based tool that includes computer code designed to validate data at the time of data entry (preventing logical errors) and incorporate branching logic (ensuring only relevant questions are asked). Examples of data collected include demographics; location and nature of procedure performed; nil per os (NPO) status; use of adjunctive medications; and the presence or absence of adverse events and related interventions. Quality oversight and case auditing by the primary investigator for each participating site and the lead project investigator (J.C.) includes submission of ≥90% of cases from contributing locations and minimum case entry review every 6 months to minimize selection bias and to ensure data integrity.

We evaluated patients ≤21 years of age who received N_2O as their primary sedative during the study period. A preparatory survey of PSRC members revealed that some institutions used N_2O to facilitate intravenous (IV) line placement, then discontinued N_2O and used a different sedative to perform the procedure, but still documented N_2O as part of the sedation. Therefore, we selected for cases that used N_2O as the primary sedative by excluding cases from analysis that included other sedatives that were more likely to have been the primary sedative (ie, inhaled anesthetics, infusions of any kind, propofol, ketamine, or dexmedetomidine).

Data Analyses

Descriptive measures were used to evaluate the characteristics of patients, sedations, and associated adverse events. Adverse events included vomiting, unable to achieve sedation needed to complete procedure, and serious adverse events, defined as airway obstruction (lack of air movement in spite of respiratory effort requiring sustained support or airway device insertion to maintain air exchange); desaturation; apnea; laryngospasm; aspiration; unplanned admission; cardiac arrest; emergency call for anesthesiologist; unplanned intubation; or death.

Predictors of adverse events were identified using a multivariable logistic regression model. Predictors were selected a priori based on previously demonstrated, or clinically plausible, relevance, and included age <4 years; weight <10 kg; sex; American Society of Anesthesiologists (ASA) status ≥3; coadministration of any opioid and/or benzodiazepines; and NPO full meals <6 hours and NPO clear liquids <2 hours.[6,20,21] Concentration of N_2O was not included because the variable was introduced into the database November 2012, and missing for 31% of cases at time of analysis. Bivariate analysis using Pearson χ^2 test was conducted for each predictor and adverse event; predictors with $P < .1$ were included in the regression model.

We performed statistical analyses with STATA (v 11.2; StataCorp, College Station, Texas).

Results

During the 32-month study period, we identified 1634 cases from 22 PSRC sites that used N_2O as the primary sedative. Patient characteristics are shown in Table I. Almost all children were ASA 1 and 2, and approximately one-half had no coexisting problems. One-third of patients were NPO full meals >8 hours, but about 90% were NPO full meals >6 hours.

Sedation and procedure characteristics are shown in Table II. Approximately 90% were performed in sedation units, emergency departments (EDs), and radiology departments; 89% were performed by advance practice nurses and physician assistants, intensivists, and pediatric emergency physicians; and about 90% of procedures were considered painful. Only 68.9% of procedures documented the highest concentration of N_2O administered. Of these cases, 7.9% used <50%, 31.6% used 50%, and 60.5% used >50%. Most patients were monitored by direct observation and/or pulse oximetry, and almost one-third (28.6%) did not have any cardiopulmonary monitoring. The benzodiazepines administered were exclusively midazolam, and the most common opioid was fentanyl (66.3%). About

Table I. Patient characteristics (n = 1634)

	n	%
Age (median 7 y; IQR 5, 11; range <1 mo to 21 y old)		
<4 y old	242	14.8
4 to <8 y old	578	35.4
8 to <12 y old	424	25.9
≥12 y old	390	23.9
Weight (median 26.4 kg; IQR 18.5, 43; range 5-181 kg)		
<10 kg	27	1.6
10 to <40 kg	1136	69.5
40 to <70 kg	351	21.5
≥70 kg	120	7.4
Sex, female	954	58.4
ASA status		
1	670	41.1
2	897	55.1
≥3	62	3.8
Missing	5	
Coexisting problems		
Neurologic	185	11.3
Metabolic/genetic	89	5.5
Developmental delay	75	4.6
Asthma	62	3.8
GI	53	3.2
Renal	51	3.1
Hematologic/oncologic	30	1.8
Psychiatric	23	1.4
Cardiovascular	22	1.4
Other (all that are <1%)	179	11
None	865	52.9
NPO status		
Clear liquids <2 h	82	5.3
Missing clear liquids data	79	
Nonfat solids <6 h	178	11.4
Missing nonfat solids data	76	
Full meals <6 h	161	10.4
Full meals <8 h	968	62.2
Missing full meals data	79	

GI, gastrointestinal.