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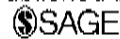
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Original Article

Deep Sedation With Propofol in Patients With Rett Syndrome

Nancy M. Tofil, MD; Mark A. Buckmaster, MD; Margaret K. Winkler, MD, FCCM; Beth H. Callans, RN; Monica P. Islam, MD; Alan K. Percy, MD

ABSTRACT

Herein we present the largest retrospective case-control series of deep sedation in patients with Rett syndrome, including discussion of the unique aspects of Rett syndrome that make these patients at high risk for sedation. Twenty-one patients with Rett syndrome and 21 control patients who received propofol for deep sedation to facilitate lumbar puncture were compared. Patients with Rett syndrome required significantly less propofol than control patients when standardized for weight and the duration of the procedure ($P = .004$). Seven of the 21 patients with Rett syndrome compared with none of the control patients experienced a serious adverse event, most of which were due to prolonged apnea ($P = .004$). All adverse events were transient, and all patients returned to their baseline after the procedure was completed. Sedation of patients with Rett syndrome is associated with a relatively high rate of complications and should not be done without appropriate personnel available who recognize the risks of sedating this unique population. (*J Child Neurol* 2006;21:857-860; DOI 10.2310/7010.2006.00051).

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From the Department of Pediatrics, Divisions of Critical Care (Drs Tofil, Buckmaster, and Winkler and Ms Callans), Anesthesia (Dr Buckmaster), and Neurology (Drs Islam and Percy), The University of Alabama at Birmingham, Birmingham, AL.

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Address correspondence to Dr Nancy Tofil, 1600 7th Avenue South, ACC 504, Birmingham, AL 35233. Tel: 205-939-9387; fax: 205-975-6505; e-mail: ntofil@peds.uab.edu.

Rett syndrome is a neurodevelopmental disorder that primarily affects girls. These patients have a myriad of problems, some of which require radiographic or invasive procedures for diagnosis and management. Because of their profound cognitive impairment, deep sedation is often required for successful completion of these procedures. Herein we present the largest series regarding the use of deep sedation in this unique population.

Rett syndrome was described originally in 1966 by Andreas Rett but was not known worldwide until 1983, when Hagberg reported 35 girls affected with autism, dementia, ataxia, and loss of purposeful hand movements.^{1,2} For girls, Rett syndrome is a significant cause of neurodevelopmental disability, with a prevalence of 1 in 10,000 to 20,000, and is the leading cause of profound cognitive impairment.³⁻⁵ The clinical criteria for the diagnosis of classic Rett syndrome were developed initially in the 1980s and recently updated.⁶⁻⁸ These criteria include an apparently normal pre- or perinatal period and first 6 months of life. Over the following months, there is loss of developmental skills, which progresses to severe mental retardation and characteristic hand-wringing movements. Recently, molecular diagnosis has become available with mutation analysis for the defective gene in Rett syndrome, *MECP2*, which encodes the methyl-cytosine-guanosine (CpG) binding protein 2.⁹

Patients with Rett syndrome often require procedures such as magnetic resonance imaging (MRI), positron emission tomography (PET), and lumbar puncture for diagnostic or therapeutic purposes. Owing to their limited mental capabilities, many of these patients require deep sedation for these procedures to be completed successfully.¹⁰⁻¹³

Many different agents can be used for deep sedation in pediatric patients. Common agents include propofol, ketamine, midazolam, and fentanyl.¹³⁻¹⁶ Each of these agents has a relatively rapid onset and a short duration of action and is titratable to the desired level of consciousness, which provides a favorable safety profile. However, many of these agents have potentially serious side effects, including apnea, hypotension, and upper airway obstruction.^{13,17-19} Patients who have neurologic abnormalities or abnormal upper airways can be more likely to experience problems with deep sedation than other patients.

Many unique features in patients with Rett syndrome make them especially prone to experience serious adverse side effects from deep sedation. These problems include scoliosis, episodic hyperventilation, breath holding, bloating, and central autonomic dysfunction.

Although deep sedation in pediatrics is becoming more common, there are no published reports on the safety of deep sedation in patients with Rett syndrome.¹⁷ This is a unique population of patients, and it is important to understand their response to sedation. Although Rett syndrome is a relatively rare pediatric syndrome, many of the features in Rett syndrome that place them at a higher sedation risk are present in other, more common neurologic conditions, such as cerebral palsy. We report our experience with 21 patients with Rett syndrome who underwent a lumbar puncture as part of a research protocol and received deep sedation.

METHODS

As part of a separate research study, patients with Rett syndrome were recruited to undergo an elective lumbar puncture for a detailed analysis of cerebrospinal fluid. All of these patients received propofol to facilitate this procedure. Separate informed consent was obtained from each patient's family for the research study, lumbar puncture, and deep sedation. The Institutional Review Board of The University of Alabama at Birmingham approved both the original research study and this case-control study on deep sedation.

Study Design

The study design was a retrospective chart review of 21 case-control pairs. We compared the rate of serious adverse events in patients with Rett syndrome versus a control population. Serious adverse events were defined as the need for bag-valve-mask ventilation, prolonged apnea (> 30 seconds), bradycardia (heart rate < 60 beats per minute), and hypotension (systolic blood pressure < 70 mm Hg + [age in years × 2]).²⁰

Scoliosis was assessed in all patients with Rett syndrome but was not assessed in control patients. Mild scoliosis was defined as a Cobb angle of 1 to 20 degrees, moderate as a Cobb angle of 21 to 40 degrees, and severe scoliosis as a Cobb angle greater than 40 degrees.

Our control population was randomly selected from our sedation database and matched for procedure, sex, age, and weight. Our database contains over 3500 patients and includes all patients who have received deep sedation from our sedation service at The Children's Hospital of Alabama since it began in 2000. This sedation service is staffed by pediatric intensivists. Three different physicians sedated the patients with Rett syndrome, with each physician performing between five and nine of the sedations. Six physicians sedated the control patients. The three physicians who sedated the patients with Rett syndrome were responsible for sedating the majority of the control patients (16 of 21). All patients who were sedated with Rett syndrome and matched controls were included in the data analysis.

Statistical Analysis

All statistical analyses were performed using SPSS, version 11.5 (SPSS Inc, Chicago, IL). A comparison of means for interval data was done using an unpaired Student's *t*-test; for ordinal data, a chi-square test was used. Data for scoliosis were distributed in none, mild, moderate, and severe categories and compared using analysis of variance. All tests were two-tailed. A *P* < .05 was considered statistically significant.

RESULTS

There were no differences in age, weight, gender distribution, or the procedure performed between the patients with Rett syndrome and the control group. All patients in both groups were female, and all patients had only a lumbar puncture performed. Population demographics are shown in Table 1.

Scoliosis was very prevalent in patients with Rett syndrome; however, it was not assessed in controls. Ten patients (48%) had mild scoliosis, two (9.5%) had moderate scoliosis, and one (5%) had severe scoliosis. Only eight patients with Rett syndrome (38%) had no evidence of scoliosis.

Patients with Rett syndrome were statistically more likely to have a serious adverse event than control patients (Table 2). Seven of the 21 patients with Rett syndrome had a serious adverse event, whereas none of the 21 control patients experienced an

adverse event. Seven patients with Rett syndrome had prolonged apnea. Two of these patients required bag-valve-mask ventilation, and one patient experienced bradycardia. Patients with Rett syndrome had a significantly lower dose of propofol when standardized to the patient's weight and the duration of the procedure. Neither the degree of scoliosis nor the presence or absence of scoliosis was associated with adverse events.

DISCUSSION

Rett syndrome is an interesting neurodevelopmental disorder that predominantly affects girls. It often presents with loss of developmental milestones and loss of purposeful hand movements. Clinical criteria have been developed and recently updated for the diagnosis of classic Rett syndrome.⁶⁻⁸ A clinical staging scheme was developed in 1986 to describe the clinical stages that evolve with increasing age in these patients. Stage I (early-onset stagnation) begins by 6 to 18 months of age with loss of acquired developmental skills, particularly involving speech and hand movements. Stage II (developmental regression), which can last for many months, begins by 1 to 4 years of age, with further loss of acquired skills and mental deficiency. Stage III (pseudostationary period) can last for many years and is marked by a plateau of developmental regression, with some improvement in communication skills. Stage IV (late motor deterioration) is characterized by more severe neuromuscular disability with deterioration in ambulation and commonly includes progressive scoliosis. Other associated symptoms of Rett syndrome include stereotypic hand movements, intensive eye communication, episodic hyperventilation and breath holding, bloating, and hypoplastic red-blue cold feet.³⁰⁻³²

Rett syndrome has many features that put these patients at higher risk of deep sedation. At the same time, many of the features of Rett syndrome necessitate sedation for successful completion of medical procedures. We had the unique opportunity to study a large population of patients with Rett syndrome undergoing deep sedation with propofol to facilitate a lumbar

puncture. We compared these patients with a control group that was matched for age, sex, weight, and procedure. One previous case report suggested that lower doses of anesthesia were needed for patients with Rett syndrome.²¹ On average, our patients with Rett syndrome received less propofol per unit of time than the control patients ($P = .004$). In spite of requiring less medication for sedation, there were significantly more serious adverse events in the patients with Rett syndrome than in the control patients. Most of these adverse events were related to prolonged apnea, two of which required bag-valve-mask ventilation. Despite these adverse events, all patients in both groups had their procedure successfully completed and all patients recovered to their baseline after completion of the procedure.

There are several possible reasons why patients with Rett syndrome had more serious adverse events associated with deep sedation than control patients. Significant and progressive scoliosis occurs in 36% to 100% of patients with Rett syndrome. The onset of scoliosis is often before the age of 8 years and is progressive with age.²² Significant scoliosis can lead to restrictive lung disease, with reduced compliance and reduced functional residual capacity.²³ Lung volumes and compliance are inversely related to the degree of the scoliosis curvature.²⁴ Pulmonary function tests to assess the degree of lung disease prior to deep sedation are difficult to obtain owing to the inability of most patients to cooperate with testing. However, neither the presence of scoliosis nor the degree of scoliosis correlated with an adverse event in our study. One patient in our study had severe scoliosis and did experience an adverse event. It is unclear how the results might have changed if more of our patients had severe scoliosis.

A second important feature of Rett syndrome that can lead to more adverse effects from deep sedation is a tendency for episodic hyperventilation and breath holding.^{30,36} Episodes of irregular breathing can result in arterial desaturation and even loss of consciousness.²⁷ However, this generally occurs only in the awake patient and did not appear to play a role in any of our patients' serious adverse events.

Bloating and air swallowing are also very common in Rett syndrome and can lead to gaseous distention of the stomach and intestines. This can cause an increased risk of perianesthesia vomiting and potential aspiration. Owing to the elective nature of our study, all of our patients had nothing to eat or drink for at least 8 hours prior to the procedure. No episode of vomiting occurred in either the patients with Rett syndrome or the control patients.

Finally, the known central autonomic abnormalities in girls with Rett syndrome are likely to increase their sensitivity to the

Table 1. Demographics

Variable	Rett Syndrome (Mean \pm SD)	Control (Mean \pm SD)
Age (mo)	122 \pm 76	111 \pm 52
Weight (kg)	27.8 \pm 15.7	36.0 \pm 17.6
Female, n (%)	21 (100)	21 (100)
Lumbar puncture performed, n (%)	21 (100)	21 (100)

Table 2. Outcome Data

Variable	Rett Syndrome, n (%)	Control	P
Serious adverse event	7 (33.3)	0 (0)	.004*
Bag-valve-mask ventilation	2 (10)	0 (0)	.147
Bradycardia	1 (4.8)	0 (0)	.311
Prolonged apnea	7 (33.3)	0 (0)	.004*
Dose of propofol (mg/kg)	2.8 \pm 1.2	3.5 \pm 1.6	.146
Duration of procedure (min)	10.8 \pm 6.6	8.6 \pm 8.5	.359
Dose of propofol per time (μ g/kg/min)	310 \pm 160	520 \pm 270	.004*

*indicates $p < 0.05$.

respiratory depressant effects of common sedatives and anesthetics. Many experts believe that the brainstem function of patients with Rett syndrome is immature and might be a factor in causing unexpected sudden death in some patients.^{25,26,28-30} This feature might have played a role in our patients with prolonged apnea.

This is the largest study to date documenting the effects of deep sedation in patients with Rett syndrome.^{21,23,31,32} Previous studies have all been case studies or small case series that showed the relative safety of anesthesia in patients with Rett syndrome. Our study demonstrates that a relatively high rate of adverse events occurs in patients with Rett syndrome receiving deep sedation.

CONCLUSION

Deep sedation is becoming more common in pediatrics. It will be important to monitor the safety of this practice, especially in high-risk patient populations. Specifically, patients with Rett syndrome are at increased risk of sedation-related transient adverse events. Most adverse events are related to prolonged apnea and airway compromise. Patients with Rett syndrome should not be sedated without appropriate personnel available who are skilled to intervene and who recognize the risks involved with sedating this unique population.

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