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*Review article*

# *Anesthesia and Prader–Willi syndrome: preliminary experience with regional anesthesia*

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## *Summary*

The constellation of neonatal hypotonia, developmental delay, hypogonadism and obesity caused by hyperphagia was first reported in 1956 and subsequently termed Prader–Willi syndrome (PWS). Genetic analysis has demonstrated abnormalities of chromosome 15. Anesthesia concerns of PWS include morbid obesity, the potential for difficulties with airway management, risk for perioperative respiratory failure, abnormalities in the central control of ventilation and temperature, rare reports of primary myocardial involvement, aggressive and at times violent behavior and glucose intolerance. For the first time, we report the use of regional anesthesia in four patients with PWS. A lumbar plexus catheter was used to provide postoperative analgesia in one patient while regional anesthesia (fasica iliaca block, spinal anesthesia, and lateral vertical infraclavicular block) was used to provide primary intraoperative anesthesia in three other patients while avoiding the need for general anesthesia. Previous reports of the anesthesia care of patients with PWS are reviewed and the potential perioperative implications of the sequelae of PWS are discussed.

***Keywords:*** Prader–Willi syndrome: anesthesia; regional

## Introduction

The constellation of neonatal hypotonia, developmental delay, hypogonadism and obesity caused by hyperphagia was first reported in 1956 by Prader, Labhart and Willi and subsequently termed Prader–Willi syndrome (PWS) (1). Genetic analysis has demonstrated that many of these patients have abnormalities of chromosome 15, most often a deletion affecting the proximal portions of the long arm (15q11-13) (2,3). Although the exact incidence of PWS is unknown, it may be as common as trisomy 21 (4). Patients with PWS frequently present for anesthesia related to associated congenital anomalies or developmental orthopedic deformities including scoliosis, hip dysplasia and lower limb alignment problems. We present four patients with PWS who presented for various orthopedic procedures and review the perioperative care of such patients. Although the anesthesia care of such patients has been previously reported, we are not aware of

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previous reports outlining the use of regional anesthesia, which was used for postoperative analgesia in one patient and as the primary anesthetic in three other cases.

## Case reports

### *Patient 1*

A 9-year-old boy (78 kg) with PWS presented for open reduction and internal fixation of the right hip. His past history was noncontributory and was negative for previous anesthetics. Physical examination revealed an obese male in no acute distress with a Mallampati grade II airway. The patient was held *nil per os* for 6 h. A 22-gauge peripheral i.v. cannula was placed on the ventral aspect of the left wrist. Ranitidine (50 mg) and metoclopramide (5 mg) were administered i.v. 1 h prior to anesthesia induction. The child was premedicated with intravenous midazolam (2 mg) and routine monitors were placed. Anesthesia induction included propofol (2 $mg \cdot kg^{-1}$) followed by rocuronium (0.4 $mg \cdot kg^{-1}$) to facilitate tracheal intubation. Because of limited peripheral venous access, a central line was placed using the Seldinger technique into the right internal jugular vein. Maintenance anesthesia was provided by isoflurane (expired concentration 1–2%) and fentanyl (3 $\mu g \cdot kg^{-1}$). The surgical procedure lasted 160 min. At the completion of the surgical procedure, a lumbar plexus catheter was placed using an insulated Tuohy needle and a nerve stimulator. An initial bolus of 25 ml of 0.375% levobupivacaine was given, followed by an infusion of 0.15% levobupivacaine at 10 $ml \cdot h^{-1}$. After placement of the lumbar plexus catheter, the patient's trachea was extubated. The postoperative course was complicated by an oxygen requirement for 36 h because of right-sided atelectasis, which cleared with chest physiotherapy and incentive spirometry. He was discharged home on postoperative day 6.

### *Patient 2*

A 4-month-old infant (6.2 kg) presented with persistent hypotonia from birth and lack of achievement of developmental motor milestones. The work-up including chromosomal analysis resulted in the diagnosis of PWS; however, given the severity of the hypotonia, a muscle biopsy was scheduled to rule out additional pathology. Apart from hypotonia, the physical examination was unremarkable. She was held *nil per os* for 4 h. After application of topical anesthetic cream, a peripheral i.v. cannula was placed and maintenance intravenous fluids started. The infant was brought to the operating room and routine monitors were placed. Supplemental oxygen was provided via nasal cannula at 2 $l \cdot min^{-1}$. Following the administration of glycopyrrolate (10 $\mu g \cdot kg^{-1}$), sedation was provided by incremental doses of ketamine (0.25 $mg \cdot kg^{-1}$) to a total dose of 1.25 $mg \cdot kg^{-1}$. After sterile preparation, a fascia iliac block was placed using a 1″, 24-gauge blunt-end block needle. When correct needle location was achieved, 4 ml of 0.375% levobupivacaine was injected. A muscle biopsy was performed while the infant breathed spontaneously. No additional sedation or analgesia was required during the surgical procedure lasting 35 min. The postoperative course was unremarkable and she was discharged home the following morning.

### *Patient 3*

An 18-month-old infant (11.1 kg) with a diagnosis of PWS presented for unilateral clubfoot repair. The medical history revealed a delay in the achievement of motor and speech milestones and he had not started walking. There had been no previous surgical procedures. Physical examination was unremarkable except for mild hypotonia. He was held *nil per os* for 4 h. After application of topical anesthetic cream, a peripheral intravenous cannula was placed and maintenance intravenous fluids started and he was brought to the operating room where routine monitors were placed. Supplemental oxygen was provided via nasal cannula at 2 $l \cdot min^{-1}$. Following the administration of glycopyrrolate (10 $\mu g \cdot kg^{-1}$), sedation was provided by incremental doses of ketamine (0.5 $mg \cdot kg^{-1}$) to a total dose of 1.5 $mg \cdot kg^{-1}$. He was held in the sitting position and after sterile preparation, a lumbar puncture was performed at the $L_{3-4}$ interspace using a 1.5″, 22-gauge spinal needle. After free flow of cerebrospinal fluid was obtained, 5 mg of tetracaine in $D_{10}W$ with an epinephrine wash were injected. A $T_{8-10}$ spinal anesthetic level was obtained. A tourniquet was placed and the surgical procedure

 

completed without difficulty. Surgical time was 75 min. No additional analgesic or sedative agents were administered. The postoperative course was unremarkable and he was discharged home on postoperative day 2.

### *Patient 4*

A 12-year-old boy (84 kg) with PWS presented for open reduction and internal fixation of the right forearm to treat a deformity injury from a previous fracture. His past history was noncontributory and had no previous anesthetics. Physical examination revealed an obese male in no acute distress with a Mallampati grades II–III airway. The patient was held *nil per os* for 6 h. A 22-gauge peripheral i.v. cannula was placed on the ventral aspect of the left wrist. Ranitidine (50 mg) and metoclopramide (10 mg) were administered i.v. 1 h prior to anesthesia induction. After the placement of routine monitors, glycopyrrolate (0.2 mg) and midazolam (2 mg) were administered i.v. followed by incremental doses of ketamine (25 mg) to a total of 100 mg. After sterile prep and drape, brachial plexus blockade was achieved using a lateral vertical infraclavicular approach. Once correct needle placement was achieved, 30 ml of 0.5% levobupivacaine with clonidine (40 μg) were incrementally injected. Adequate surgical anesthesia was achieved in the distribution of the ulnar, median, radial, and musculocutaneous nerves. The surgical procedure lasted 130 min. At the completion of the surgery, he was transported to the postanaesthesia care unit. The postoperative course was uncomplicated and he was discharged home the following day.

## Discussion

Prader–Willi syndrome is recognized as the most common cause of genetically inherited obesity with a reported prevalence of approximately 1 in 25 000 births (5). However, because of the nonspecific and often subtle characteristics of the syndrome at an early age, it may be underdiagnosed and an incidence of 1 in 10 000–15 000 is possibly a more accurate estimate (6,7). There is an equal frequency in both sexes and all races. PWS is the first human genetic disorder associated with genomic imprinting and uniparental disomy (UPD) (5). Genomic imprinting refers to the differential expression of genetic material depending on the parent of origin and UPD describes the inheritance of both copies of a chromosome from a single parent.

Prader–Willi syndrome results from the absence of normally active paternally inherited genes at chromosome 15q11-13 (2,3,5). There are three known mechanisms by which these paternally imprinted genes are abolished. The most common mechanism, affecting 70–75% of patients, is a deletion of the paternally inherited 15q11-13 region. More recently, this deletion has been further categorized into two groups according to the area of the breakpoint. The larger, more proximal type I deletion accounts for approximately 40% of those in the deletion subgroup with the smaller, more distal type II deletion accounting for the other 60%. This distinction may be of relevance to caregivers as it has been shown that certain maladaptive behavior may be more prevalent in type I individuals than type II individuals (8). The second most common mechanism, affecting 20–25% of patients, is maternal UPD in which both copies of chromosome 15 are maternally derived. The remaining 1–5% show an imprinting center defect of chromosome 15 resulting in an abnormal methylation pattern with subsequent altered gene expression (9). Despite the many advancements, the majority of specific genes in the 15q11-13 region that may be responsible for the phenotypic effects of the syndrome have not yet been identified. Two genes that have been described are the small nuclear ribonucleoprotein polypeptide N (*SNRPN*) and *necdin*. Both genes are involved with brain functioning and are thought to play a critical role in the hypothalamic and respiratory abnormalities seen in PWS, respectively (10–12).

Prader–Willi syndrome is a complex disorder illustrated by an impressive array of clinical manifestations, most of which are believed to result from a functional deficiency of various hypothalamic systems. Among the more prominent findings are obesity, hypotonia, hypogonadism, short stature, developmental delay, maladaptive types of behavior, mental retardation and characteristic dysmorphic facies (5,13). The clinical picture of PWS has classically been described as a two-stage disorder consisting of an infancy phase followed by a childhood phase (6). This classic two-stage model has been expanded upon by some authors to include

four stages with the addition of an initial fetal–neonatal stage and a fourth, adolescent phase in order to further delineate the changing clinical picture (14,15). The infancy phase is dominated by hypotonia, which invariably has a prenatal onset and results in poor sucking and swallowing reflexes with subsequent 'failure to thrive' which frequently requires special feeding techniques such as gastrostomy tube placement. Other prominent features of this phase include a weak cry, lethargy and developmental delay including both language and motor deficits. Hypogonadism is evident in infancy manifested as genital hypoplasia with cryptorchidism and becomes more evident in adolescence with delayed pubertal development. The childhood phase begins at 2–4 years of age and is characterized by hyperphagia subsequently leading to obesity. Like the hypogonadism, hypothalamic dysfunction is believed to be primarily responsible for the hyperphagia owing to dysfunction of central satiety centers (13). As the child progresses through childhood and into adolescence, cognitive and behavioral problems emerge as the predominant findings. Most patients with PWS can be classified as being mildly mentally retarded with an Intelligent Quotient (IQ) of 60–70. Characteristic behavior during this period include temper tantrums, oppositional and obsessive–compulsive behavior and withdrawal. As the child enters adolescence, the maladaptive behavior can become more aggressive with lying and stealing which are usually associated with food-seeking endeavors (5,10,14–16). Other common, but variable, characteristics include hypopigmentism, strabismus, and skin picking. Findings of particular interest when considering the perioperative management of these patients include a characteristic dysmorphic facial appearance, scoliosis/kyphosis, temperature regulatory abnormalities, sleep disturbances, high pain threshold, viscous saliva, metabolic disturbances and a high threshold for vomiting (see below) (10,17).

Early clinical diagnosis remains elusive because of nonspecific and subtle findings at birth and during infancy. A widely accepted set of diagnostic criteria have been developed to aid in the clinical diagnosis of PWS (6). The system includes eight major and 11 minor criteria and is based on a point system in which the score requirements for diagnosis vary according to age. More recently, a set of revised criteria have been proposed with the intent of prompting a lower threshold for pursuing definitive diagnostic testing (18). Genetic testing in the form of fluorescence *in situ* hybridization and methylation studies are now widely available and have become the gold standard for a definitive diagnosis of PWS (18). The sequelae that result from obesity are the most common causes of early morbidity and mortality in PWS patients. These sequelae include respiratory failure, cardiovascular diseases, diabetes mellitus and sleep apnea (19). Therefore, early diagnosis and intervention are of paramount importance in preventing obesity and thus halting the common causes of premature illness and death in these patients (20). It has been proposed that any newborn or infant with unexplained hypotonia or feeding difficulties be genetically tested for PWS (18).

The invariable features of hypogonadism and hyperphagia lead to the presumption that hypothalamic dysfunction is the primary defect of PWS. However, no structural deficits have yet been discovered. The potential therapeutic impact of growth hormone (GH) treatment has been studied extensively. GH has been shown to improve behavioral problems, body composition, sleep quality, linear growth and may improve central respiratory drive (21,22). Although GH is now considered fundamental in the care of children with PWS, it is currently indicated only for documented growth failure and additional studies are needed to evaluate the impact of long-term therapy (23).

Given the prevalence of this disorder and the likelihood of surgical intervention to treat its associated endorgan effects, anesthesia care is frequently required in patients with PWS. Previous reports regarding anesthesia and the potential perioperative complications of patients with PWS are summarized in Table 1 (24–31). In distinction to these previous reports, we report for the first time the use of regional anesthesia as a successful technique for providing postoperative analgesia in one patient and as the primary anesthetic in three other patients. The regional techniques used as a primary anesthetic included spinal anesthesia and two periperhal nerve blocks (fascia iliaca block and lateral vertical infraclavicular block). In our first patient, given the need for central venous access, the anticipated duration of the surgical procedure, and the intraoperative

 

**Table 1**
Reports of anesthesia in patients with Prader–Willi syndrome

| *Authors* | *Patient* | *Procedure* | *Pertinent findings* |
|---|---|---|---|
| Palmer and Atlee (24) | 8.5 years, male | Bilateral orchiopexy | Multiple dental carries requiring removal of a loose tooth prior to intubation. Small glottis with redundant epiglottis. Mention of previous dental procedure with severe postoperative hypoglycemia and generalized tonic–clonic seizure. |
| Milliken and Weintraub (25) | 10 years, male | Bilateral orchiopexy | First case aborted due to ventricular arrhythmia and tachycardia to 250 $b \cdot min^{-1}$ and tachycardia with premature ventricular contractions (PVCs) postoperatively. Second attempt resulted in hypertension, bigeminy and tachycardia intraoperatively and postoperative hypertension tachycardia |
| Yamashita *et al.* (17) | 7 months, male | Bronchoscopy | Tachycardia during intubation and maintenance. Postoperative dyspnea and cyanosis with fever for 2 days |
| | 8 years, female | Pacemaker placement | Bradycardia with irregular rate right bundle branch block (RBBB) during intubation. Fever for 1 week postoperatively |
| | 10 years, female | Cholecystectomy | PVCs on induction with left axis deviation on ECG. A high-arched palate |
| | 11 years, male | Bilateral orchiopexy | Fever on postoperative day 1 |
| Mayhew and Taylor (26) | 6 years, male | Bilateral orchiopexy | Uneventful anesthetic care |
| | 3 years, male | Bilateral orchiopexy | Difficult intubation (no explanation), MH picture with rapid temperature rise and acidosis. The procedure was aborted and the second attempt was uneventful with pancuronium instead of succinylcholine for intubation |
| Mackenzie (27) | 2 years, male | Correction of ventral curvature of micropenis | Uneventful anesthetic care |
| | 18 years, male | Removal of excessive thigh tissue | Uneventful anesthetic care |
| Sloan and Kaye (28) | 17 years, female | Dental rehabilitation | Regurgitated gastric secretions into mouth during intubation despite being *nil per os* for 10 h |
| Dearlove *et al.* (29) | 16 months, female | Plaster cast for scoliosis | Uneventful anesthetic care; however, the mother returned on postoperative day 5 with complaints of night-time apnea. The authors speculated that this may have been related to the application of a plaster body cast in a hypotonic patient and not necessarily residual anesthetic effects |
| Tseng *et al.* (30) | 5 years, male | Tonsillectomy and uvulopalatopharyngoplasty | Postoperative tachypnea and oxygen desaturation to 70% requiring reintubation and ICU admission |
| | 4 years, male | Prolapsed rectum | Transient intermittent bronchospasm with hypercapnia during emergence. Aggressive postoperative behavior |
| Lirk *et al.* (31) | 4 years, male | Laparoscopic orchiopexy | Uneventful anesthetic care |
| | 4 years, male | De-rotation/fixation of scoliosis | Uneventful anesthetic care |
| | 4 years, male | Tonsillectomy | Delayed onset of spontaneous breathing at emergence |
| | 22 years, male | Dental surgery | Aggressive behavior requiring induction with i.m. ketamine. Short neck with limited mobility requiring fiberoptic intubation. Difficult oxygenation due to bronchospasm requiring high peak inspiratory pressures |

positioning (lateral decubitus) without ready airway access, we opted for the use of general anesthesia and the placement of the lumbar plexus catheter for postoperative analgesia. However, the use of a pure regional anesthetic technique may have been feasible utilitizing either a spinal or a combined lumbar

 

plexus/sciatic nerve block. Although successful in our series of four patients, we would concede that a larger series is necessary to definitely document the safety and efficacy of regional anesthesia as the primary technique in this patient population. A risk : benefit ratio must considered when using regional anesthesia plus sedation in patients with PWS who may be at higher risk of aspiration than the general pediatric population.

In addition to the other manifestations of the disorder, of primary concern to the anesthesiologist is the invariable association of morbid obesity and its antecedent perioperative risk factors including airway difficulties, aspiration risk, poor vascular access and intraoperative positioning issues. Regional anesthetic techniques may have a role in such patients by eliminating the need for general anesthesia and its perioperative risks in patients with obesity, hypotonia, respiratory dysfunction and the other associated features of PWS. Given the invariable association of developmental delay in PWS (see below), sedation will be required not only for block placement, but also to ensure a cooperative patient during the surgical procedure. We chose ketamine for its limited effects on respiratory function as well as its ability to provide both sedation and analgesia. Especially in older children, ketamine should be coadministered with either propofol or a benzodiazepine to limit the potential for emergence phenomena.

As with many of the syndromes in infants and children, there have been reports of airway difficulties in patients with PWS including problems with tracheal intubation reported by three different authors (Tables 1 and 2) (24,26,31). Airway management may be further complicated by the frequent association of poor dentition, micrognathia, palatal abnormalities, and limited neck mobility. Although we noted no problems with airway management in our series of patients, tracheal intubation was performed in only one of the patients. In the two patients who would cooperate with the examination, airway examination revealed a Mallampati grade II or III view. Therefore, in such patients the appropriate equipment to deal with the 'cannot intubate/cannot ventilate' scenario should be readily available. In our patients in whom regional anesthesia was performed, we had ready access to such equipment including an opened and ready-to-use LMA should airway difficulties occur.

Intraoperative and postoperative respiratory compromise have also been a frequent perioperative problem in patients with PWS. Lirk *et al.* reported bronchospasm and poor oxygenation with the need to use high peak inspiratory pressures in one patient (31) while Tseng *et al.* noted intermittent bronchospasm, stridor, oxygen desaturation, and hypercapnia which required reintubation in one patient and intraoperative bronchospasm with hypercapnia in their other patient (30). The first patient in our series had a complicated postoperative course from right-sided atelectasis requiring supplemental oxygen for 36 h. Even outside the perioperative period, respiratory disease can be significant source of morbidity and mortality in patients with PWS in both the early and late phases of the syndrome. The onset of such problems may occur in the neonatal period and require prolonged neonatal ventilatory support (32). Respiratory abnormalities as a result of hypotonia leading to hypoventilation with subsequent respiratory arrest are a major cause of death in infants and children with PWS. Younger PWS patients often succumb to severe respiratory infections as a result of aspiration due to hypotonia leading to poor pharyngeal coordination, chronic aspiration and a weak cough. Such problems may lead to sudden death following acute respiratory infections with a surprisingly short clinical course from the onset of symptoms to acute deterioration (20). During the preoperative visit, a thorough evaluation of the patient's past and current respiratory status should be undertaken. Postoperartively, aggressive pulmonary toilet with chest physiotherapy and other respiratory adjuncts to facilitate coughing and secretion clearance should be instituted. This becomes particularly relevant following upper abdominal or thoracic procedures. Older patients with PWS also commonly have pulmonary function abnormalities, usually manifest as a restrictive pattern with or without obstructive components. While obesity imposes an added mechanical load on the respiratory system and is a common cause of hypoventilation, a number of factors are believed to contribute to restrictive lung disease in these patients including obesity, thoracic muscle weakness (hypotonia) and an increased incidence of kyphoscoliosis (11).

These respiratory issues may be further compromised by defective central control of ventilatory with obstructive/central sleep apnea manifest as

 

**Table 2**
Anesthetic agents used in Prader–Willi syndrome patients

| *Author(s)* | *Patient* | *Premedication* | *Induction* | *Neuromuscular (NM) blockade* | *Maintenance* | *Emergence, NM blockade reversal* |
|---|---|---|---|---|---|---|
| Palmer and Atlee (24) | 1 | Morphine, pentobarbital, atropine | Halothane | – | Halothane, $N_2O$ | – |
| Milliken and Weintraub (25) | 1 | – | Halothane, $N_2O$ | – | – | – |
| | 2 | Secobarbital, morphine, scopolamine | Halothane, $N_2O$ | Succinylcholine | Halothane | – |
| Yamashita *et al.* (17) | 1 | – | Halothane | Succinylcholine | Halothane | – |
| | 2 | – | Halothane, $N_2O$ | Succinylcholine | Halothane, $N_2O$ | – |
| | 3 | – | Halothane, $N_2O$ | Succinylcholine | Halothane, $N_2O$ | – |
| | 4 | – | Halothane, $N_2O$ | Succinylcholine, pancuronium | Halothane, $N_2O$ | – |
| Mayhew and Taylor (26) | 1 | – | Halothane, $N_2O$ | Succinylcholine | Halothane, $N_2O$ | – |
| | 2 | – | Halothane, $N_2O$ | Succinylcholine, curare | Halothane, $N_2O$ | Atropine, neostigmine |
| | 3 | – | Thiopental | Pancuronium | Fentanyl, $N_2O$ | Atropine, neostigmine |
| Mackenzie (27) | 1 | Trimeprazine, morphine, glycopyrrolate | Halothane | Atracurium | Isoflurane, $N_2O$ | Neostigmine, glycopyrrolate |
| | 2 | Papaveretum, scopolamine | Halothane, $N_2O$ | – | Halothane, $N_2O$ | – |
| Sloan and Kaye (28) | 1 | – | Thiopental | Vecuronium | Isoflurane, fentanyl, $N_2O$ | – |
| Dearlove *et al.* (29) | 1 | – | Halothane, $N_2O$ | Atracurium | Isoflurane | – |
| Tseng *et al.* (30) | 1 | – | Propofol, sevoflurane | – | Sevoflurane | Reintubation with thiopental and vecuronium |
| | 2 | – | Thiopental, sevoflurane | Succinylcholine | Sevoflurane | – |
| Lirk *et al.* (31) | 1 | – | Fentanyl, propofol | Rocuronium | Fentanyl, $N_2O$, propofol | Theophylline to stimulate respiratory drive |
| | 2 | – | Fentanyl, thiopental, midazolam | Rocuronium | Sevoflurane, remifentanil | |
| | 3 | – | Thiopental, midazolam | Rocuronium | Sevoflurane, fentanyl | |
| | 4 | – | Ketamine, midazolam | Rocuronium | Sevoflurane, fentanyl | |

 

abnormal ventilatory responses to hypoxia and hypercapnia when awake as well as reduced arousal to these stimuli when asleep. Studies have documented that patients with PWS increase ventilation only when exposed to higher arterial $CO_2$ levels than normal controls because of decreased sensitivity of peripheral chemoreceptors to the partial pressure of $O_2$ and $CO_2$. This may represent a primary abnormality in the peripheral chemoreceptors or may be secondary to dysfunction of hypothalamic modulation of the central respiratory centers in the CNS (12). Marzullo *et al.* (33) demonstrated that compared with obese controls, PWS patients have an increased number of apneic episodes and higher hypercapnic thresholds as well as significantly more apnea–hypopnea episodes with more significant nocturnal desaturation. The etiology of sleep apnea in PWS patients is multifactorial and includes both central and obstructive components (30,34,35). The central component may be amplified by peripheral obstructive components including obesity, hypotonia, viscous saliva and micrognathia (11). Minor radiological evidence of upper airway narrowing is a common finding in PWS, as is a neck circumference of more than 40 cm, both of which are risk factors for sleep apnea (34). Tseng *et al.* reported a case of a 5-year-old PWS patient with obstructive sleep apnea (OSA) who developed severe hypoxemia shortly after emergence from general anesthesia and tracheal extubation (30). This required reintubation of the trachea and admission to the pediatric intensive care unit. Extubation was eventually accomplished with the use of continuous positive airway pressure. The authors suggested a polysomnogram as part of an individualized preoperative workup in order to establish a baseline and identify those with severe OSA as well as postoperative admission to the intensive care unit for monitoring of respiratory status. Lirk *et al.* (31) administered theophylline to stimulate central ventilatory drive in their series of patients. Dearlove *et al.* (29) reported a 16-month-old PWS patient returned by the mother on postoperative day 5 following general anesthesia reporting episodes of apnea during the previous two nights. The authors speculated that the respiratory events may have been related to the application of a plaster body case in a hypotonic patient and not necessarily the effects of residual anesthetic agents. Because of such concerns, postoperative monitoring of respiratory status is suggested until the residual effects of anesthetic agents has dissipated (36). We favor the use of regional anesthesia to provide intraoperative anesthetic care and postoperative analgesia as a means of limiting the need for opioids and general anesthetic agents.

The first phase of PWS is characterized by severe hypotonia with poor sucking, swallowing, and is marked by episodes of asphyxia and repeated aspirations (24). Although the hypotonia progressively improves with age, issues regarding airway protection and strength of cough may place these patients at risk not only for perioperative respiratory compromise, but also for aspiration during anesthetic induction. This risk may be further increased by a reduced tendency to vomit even in the presence of gastrointestinal (GI) pathology, decreased GI motility, lowered esophageal sphincter tone and reduced pulmonary reserves (28). Sloan and Kaye (28) suggest that all patients with PWS should be considered high risk for aspiration and appropriate precautions should be taken to reduce this risk including supervised preoperative fasting.

Hypotonia has prompted some authors to caution against the use of neuromuscular blocking agents in patients with PWS, especially neonates and infants in phase 1 of the syndrome. However, several reports have demonstrated the safe use of various nondepolarizing neuromuscular blocking agents including pancuronium, atracurium, vecuronium, and rocuronium without evidence of prolonged effects (17,26–28,31). Although we would suggest caution with the use of succinylcholine in the presence of hypotonia given the theoretical risk of an exaggerated hyperkalemic response, several of the reports have also demonstrated the safe use of succinylcholine in patients with PWS (17,25,26,30). Although Mayhew and Taylor (26) reported a malignant hyperthermia-like picture in one of their patients following the administration of succinylcholine and halothane, the postoperative creatinine phosphokinase level was not elevated and other than a rapid elevation of body temperature and acidosis, no other manifestations of MH were noted.

While we did not experience any perioperative cardiovascular complications in our patients, Milliken and Weintraub (25) reported intraoperative ventricular arrhythmias, tachycardia, hypertension and premature ventricular contractions (PVCs) with

 

bigeminy. Transient PVCs in one patient and bradycardia with a right bundle branch block pattern in a second patient were reported by Yamashita *et al.* during induction with halothane (17). Obesity-related complications including cardiovascular problems, diabetes mellitus, hypertension and sleep apnea are the most common causes of death in adult PWS patients as well as the general obese population. It has, therefore, been hypothesized that obesity alone is the etiology of the cardiac sequelae in adults with PWS. Patients with PWS may have an intrinsic predisposition to cardiovascular complications independent of obesity. Marzullo *et al.* (33) examined cardiovascular characteristics in body mass index-matched obese individuals with and without PWS and found that PWS does not entirely reflect the cardiovascular characteristics of obesity. Instead these patients have the modified heart geometry of the hypotrophic hypokinetic syndrome commonly seen with GH deficiency and are at high risk of coronary artery disease and impaired cardiac function. In addition, there may be cardiac abnormalities in PWS as a result of chromosome 15 microdeletions involving NR2F2 and cardiac alpha actin (ACTC) genes essential for angiogenesis and heart development (33,35). ACTC is responsible for one form of autosomal dominant dilated cardiomyopathy, which may occur in PWS patients. Pomara *et al.* report sudden death of presumed cardiac origin in a 3-year-old male with PWS in which autopsy showed contraction band necrosis associated with ventricular fibrillation (36). In addition to these other problems, sleep apnea is known to be an independent risk factor for cardiovascular disease in the general population. Cardiovascular sequelae include diastolic and systolic dysfunction, arrhythmias, hypertension, and pulmonary hypertension with subsequent cor pulmonale. Sleep apnea, therefore, may be a contributor to the cardiovascular pathology in PWS. Given such concerns, preoperative evaluation with 12-lead ECG and echocardiography may be indicated in selected patients.

Patients with PWS exhibit aberrant thermoregulatory control mechanisms, considered to be another consequence of hypothalamic dysfunction (13). Autonomic thermoregulation involves specific areas of the hypothalamus including the ventromedial hypothalamus. There are several examples of abnormal temperature control in the perioperative period in patients with PWS with reports of both hypothermia and hyperthermia thereby emphasizing the need for perioperative temperature monitoring. Yamashita *et al.* reported postoperative fever in three of four patients in their series (17). Mayhew and Taylor (26) described a 3-year-old boy with a rapid rise in body temperature following halothane and succinylcholine that required active cooling and resulted in termination of the case. The case was repeated without incident using pancuronium and intravenous anesthetic agents. It is likely the perioperative temperature instability is the result of parasympathetic dysfunction which represents the primary autonomic disturbance in PWS (37).

Most patients with PWS have mild to moderate mental retardation with mean IQs in the 60s to low 70s. A characteristic behavioral profile becomes evident in childhood consisting of a low frustration threshold with controlling and obsessive–compulsive behavior. Lying, stealing, and aggressive behavior are not uncommon. True psychosis has been reported in 5–10% of young adult PWS patients in one study (5). Lirk *et al.* (31) describe a severely retarded 22-year-old male who was highly aggressive preoperatively and had to be induced with i.m. ketamine. In another report, Tseng *et al.* (30) describe a 4-year-old male who attacked the nurses when venipuncture was attempted prior to surgery. Cognitive impairment may also be a barrier to obtaining informed consent for anesthesia and surgical procedures.

Other minor abnormalities in patients with PWS include dental issues and abnormal salivary composition. Dental issues relate to primary problems with enamel hypoplasia and secondary issues from rumination, poor dental hygiene, and the abnormal salivary secretion composition. Abnormally thick saliva is a common finding in patients with PWS and it has been shown that salivary flow is approximately 20% of normal (38). In addition, there are increased concentrations of ions and proteins relative to water in the saliva. Because of the altered composition and lowered rate of salivation, several authors have recommended avoiding the use of anticholinergic agents. These problems may result in caries and subsequent tooth decay. Poor dentition may obviously impact on airway management. Palmer and Atlee (24) described the discovery of a loose tooth just prior to intubation requiring extraction.

**Table 3**
Specific organ system involvement with Prader–Willi syndrome

| |
|---|
| Airway |
| Difficult tracheal intubation |
| Small glottic opening |
| Narrowed subglottic area |
| Redundant epiglottis |
| Limited neck mobility |
| Macroglossia |
| Respiratory |
| Hypotonia |
| Poor cough with ineffective clearance of secretions |
| Thick bronchial secretions |
| Intraoperative bronchospasm |
| Central/obstructive apnea |
| Restrictive lung disease (obesity, kyphoscoliosis) |
| Cardiovascular |
| Ventricular arrhythmias |
| Conduction defects |
| Hypertension |
| Cor pulmonale |
| Dilated cardiomyopathy |
| Central nervous system |
| Temperature instability |
| Defective central control of ventilation |
| Mental retardation |
| Aggressive and violent behavior |
| Low frustration threshold |
| Obsessive–compulsive behavior |
| Miscellaneous |
| Obesity |
| Glucose intolerance |
| Kyphoscoliosis |
| Poor dentition |
| Viscous saliva and airway secretions |

The spectrum from glucose intolerance to overt diabetes mellitus may occur in older PWS patients and is considered to be a late-appearing complication of the syndrome, appearing in the second phase (24). However, it is uncertain if this is an inherent feature of PWS or just a complication of obesity. Patients with PWS may suffer from altered regulation of fat and carbohydrate metabolism and may utilize blood glucose to manufacture fat instead of providing ongoing energy needs (24). Because of such issues, fasting during the perioperative period requires intermittent blood glucose monitoring in these patients to avoid hypoglycemia which has been reported postoperatively (26).

There are several manifestations of PWS in various organ systems which may affect perioperative care (Table 3). Of primary concern is accompanying morbid obesity as well as other primary effects of the syndrome including the potential for difficulties with airway management, risk for perioperative respiratory failure and abnormalities in the central control of ventilation (39). Although an uncommon finding in these patients, primary myocardial involvement may also occur. Other features which may impact on perioperative care include mental retardation with the propensity for aggressive behavior, glucose intolerance, and poor dentition. These features stress the importance of a thorough preoperative evaluation prior to provision of anesthesia care for these patients.

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