CASE REPORT

Dexmedetomidine and the perioperative care in Riley-Day syndrome: a case report and literature review

Matthew DiGiusto, BA*, David Martin, MD**, Joseph D. Tobias, MD**

*The Ohio State School of Medicine, Columbus, Ohio (USA)
**Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital and the Ohio State University, Columbus, Ohio (USA)

Correspondence: David Martin, MD, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio 43205 (USA); Phone: (614) 722-4200; FAX: (614) 722-4203; E-mail: David.Martin@Nationwidechildrens.org

ABSTRACT

Familial dysautonomia (FD), also known as Riley-Day syndrome, is a disorder of the autonomic nervous system that results in loss of demyelinated nerve fibers of sensory, sympathetic and parasympathetic neurons. Individuals with FD have variable clinical symptoms that may include insensitivity to pain, inability to produce tears, poor oral intake during infancy, repeated vomiting, failure to thrive, wide fluctuations in body temperature, and episodic hypertension and hypotension. These paroxysmal crises are due to dysfunction of the autonomic system with an elevation of both norepinephrine and dopamine levels. Clonidine, an α_2-adrenergic agonist, has been previously demonstrated to be an effective pharmacological agent in the treatment of dysautonomic crises related to FD. Dexmedetomidine is an α_2-adrenergic agonist with an α_2:α_1 specificity that is almost 8 times that of clonidine. The authors present the perioperative use of dexmedetomidine in a patient with FD. Previous reports of the use of dexmedetomidine in patients with FD are reviewed and the beneficial physiologic effects discussed.

Key words: Familial dysautonomia; Riley-Day syndrome; Clonidine; Dexmedetomidine; Autonomic nervous system dysfunction; Hereditary sensory and autonomic neuropathies; Paroxysmal autonomic instability with dystonia; PAID

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INTRODUCTION

Familial dysautonomia (FD), originally known as Riley-Day syndrome, was first described by Riley and Day after a constellation of unique findings were noted in a group of patients who were Ashkenazi Jews.[1] This original report included five children, whose clinical presentation included hypertension, erythematous cutaneous eruptions, excessive sweating, and defective lacrimation in response to anxiety. Today FD is recognized as one of a group of genetically distinct disorders known as Hereditary Sensory and Autonomic Neuropathies (HSAN). FD is a disorder of the autonomic nervous system that results in loss of demyelinated nerve fibers of sensory, sympathetic, and parasympathetic neurons. FD displays an autosomal recessive mode of inheritance from a single mutation on chromosome 9q31 in the gene coding inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase associated protein complex (IKBKAP).[2]

Infants with FD have variable symptoms including insensitivity to pain, inability to produce tears, poor oral intake, repeated vomiting, failure to thrive, wide fluctuations in body temperature, and episodic hypertension and hypotension.[3] Given their multiple medical problems including poor oral intake, feeding intolerance and repeated episodes of vomiting, surgical interventions may be required in these patients. Perioperatively, patients with FD may manifest paroxysmal crises, most often attributed to emotional distress or pain, which include hypertension, tachycardia, vomiting, fever, diaphoresis, and erythematous cutaneous eruptions.[3] During these paroxysmal events, norepinephrine (NE) and dopamine levels are increased.[4] It has been hypothesized that the hypertension occurring during these crises is due to the increased vascular sensitivity to released catecholamines as the blood vessels in patients with FD show an exaggerated response to NE.[5] One of the goals of perioperative care is to limit

the sympathetic stress response and blunt the release of endogenous catecholamines.

Dexmedetomidine is an α_2-adrenergic agonist approved for sedation of adults during mechanical ventilation and for monitored anesthesia care (MAC) of adults. Although FDA approved it only for use in adults, it has been used successfully in several different clinical scenarios in infants and children including sedation during mechanical ventilation, procedural sedation, supplementation of postoperative analgesia, prevention of emergence delirium, control of post-anesthesia shivering, and the treatment of withdrawal.[6] Several potential perioperative benefits of dexmedetomidine have been demonstrated including a decreased requirement for inhalational and intravenous anesthetic agents, blunting of the sympathetic stress response, decreased postoperative opioid requirements, and the prevention of postoperative shivering.[6-8] The authors report the perioperative use of dexmedetomidine in a 28-year-old patient with Riley-Day syndrome. Previous reports of the perioperative use of dexmedetomidine in patients with FD are reviewed and its effects on the sympathetic nervous system discussed.

CASE REPORT

Institutional Review Board approval for case reports involving one or two patients is not required by Nationwide Children's Hospital (Columbus, Ohio). The patient was a 28-year old, 22.5 kg female with a past medical history significant for Riley-Day syndrome, delayed psychomotor development, mental retardation, unspecified osteoporosis, and severe gastric reflux. She had a long history of breath holding spells and self-mutilation behaviors. She appeared to be approximately 7-8 years of age and was non-verbal. In May 2007 she had undergone a Nissen fundoplication with placement of a jejunostomy feeding tube to allow for enteral nutrition. A few months prior to this encounter, she was tolerating her feedings well through the gastrostomy tube, which had been placed prior to the Nissen/jejunostomy tube in 2006. She no longer required the jejunostomy tube. Therefore, the decision was made in March of 2012 to close the jejunostomy as it resulted in severe irritation of her skin. After an uneventful standard general anesthetic, the jejunostomy was closed and ultimately healed after a superficial wound infection. In the ensuing months following this procedure, the patient had significant bloating with feedings and it was decided that the best course of management was replacement of the jejunostomy tube. A review of the patient's previous anesthetics showed no prior exposure to dexmedetomidine and the clinicians used typical opiate dosing for an opiate-tolerant patient. Her long history of agitation was treated on the inpatient wards with nurse-controlled opiate analgesic strategies. On 7th postoperative day after the proximal gastrojejunostomy, an evisceration of the intra-abdominal contents was noted secondary to fascial dehiscence, necessitating a return to the operating room for exploratory laparotomy and wound closure.

Preoperative medications included dicyclomine, ranitidine, lansoprazole, inhaled budesonide and nystatin. The patient was held *nil per os* for 6 hours and was transported to the operating room where routine monitors were placed. Following pre-oxygenation, a modified rapid sequence intubation using cricoid pressure was performed with the administration of propofol 3 mg/kg, fentanyl 2.5 μg/kg and rocuronium 0.8 mg/kg. Maintenance anesthesia consisted of desflurane with an exhaled concentration of 3-5% and morphine (0.1 mg/kg). Surgical exploration revealed that the fascia on the patient's right side had failed. The remainder of the bowel was intact. The fascia was re-approximated and an nasogastric tube was placed in the gastric pouch. The surgical procedure lasted approximately 90 minutes. Intraoperative fluids included 800 mL of lactated Ringer's solution and 100 mL of normal saline. Following completion of the surgical procedure, residual neuromuscular blockade was reversed with neostigmine, administered with glycopyrrolate, and the patient's trachea was extubated. The patient was transported to the postoperative anesthesia care unit (PACU) where there were multiple episodes of breath holding resulting in decrease of the oxygen saturation measured by pulse oximetry to 50% range. These breath holding spells were self-limited with the addition of facemask oxygen support but were accompanied by significant agitation. She appeared to be at her reported baseline and therefore no additional laboratory analysis was deemed warranted at that time. Along with these episodes of oxygen desaturation, the patient had hypertension (144/91 mmHg), tachycardia (heart rate 140-160 beats/minute), diaphoresis and agitation. There was minimal change following the administration of hydromorphone (0.005mg/kg) and the initiation of a hydromophone-NCA (nurse controlled analgesia). A bolus dose of dexmedetomidine (0.4 μg/kg) was administered which resulted in a decrease of her BP to 118/80 mmHg, cessation of the diaphoresis, control of agitation, and a decrease of the heart rate to 100-120 beats/minute. She maintained her oxygen saturations $>$95% with a nasal cannula at 2 L/min of oxygen flow with a respiratory rate of 20-24 breaths/min. The patient was admitted to the Pediatric ICU and a dexmedetomidine infusion at 0.3μg/kg/hr was started, in addition to the hydromorphone-NCA. The dexmedetomidine infusion was continued for 60 hours. There were no additional episodes of hypertension, tachycardia, and

agitation; she was able to be easily weaned from dexmedetomidine at the conclusion of therapy. The remainder of her postoperative course was unremarkable and she was discharged home on postoperative day 11.

DISCUSSION

Individuals with FD present multiple intraoperative anesthetic challenges across many organ systems. Dysautonomic crisis are a common perioperative problem manifested by vomiting, diaphoresis, hemodynamic lability, bradycardia, and tachycardia. These problems can be precipitated by emotional stress, anxiety and/or pain.[3] Patients with FD have a reduction in the number of peripheral neurons in the sympathetic ganglia and a loss of sympathetic innervation of blood vessels.[9,10] Orthostatic hypotension without reflex tachycardia is common in these patients and this abnormal baroreflex may be due to a dysfunctional parasympathetic system.[11] Additional evidence for autonomic dysfunction is the presence of a prolonged QT interval in these patients.[12] Issues related to increased sympathetic outflow in patients with FD include hyperhidrosis which may result in perioperative hypovolemia and hyponatremia.[13] As such, perioperative management and control of the labile autonomic system is of utmost importance.[13,14]

Historically, diazepam has been used to control the autonomic crises of FD while more recently clonidine, an α_2-adrenergic, has been shown to be effective for refractory cases especially those manifesting hypertension.[13,14] Like clonidine, dexmedetomidine is in the imidazole subclass of the an α_2-adrenergic agonists. The α_2:α_1 specificity of clonidine is 220:1, while that of dexmedetomidine is 1620:1, making dexmedetomidine a complete α_2-agonist.[15] Additionally, dexmedetomidine has a shorter half-life (2-3 hours) compared to clonidine (12-24 hours) and is available for intravenous administration. Given its shorter half-life, it can be easily titrated by intravenous infusion while its effects dissipate more rapidly in the event of adverse effects. Additionally, there is significant experience with its perioperative use in infants and children.[6,7]

Centrally acting α_2-adrenergic agonists reduce norepinephrine release through central effects on receptors in the medullary vasomotor center. Biochemical data from a cohort of 8 adult postoperative patients demonstrate the sympatholytic effects of dexmedetomidine.[7] Following a 60 minute dexmedetomidine infusion to achieve a therapeutic plasma concentration of 600 pg/mL, the plasma norepinephrine concentration decreased from 2.1 ± 0.8 to 0.7 ± 0.3 nmol/L, the plasma epinephrine concentration decreased from 0.7 ± 0.5 to 0.2 ± 0.2 nmol/L, HR decreased from 76 ± 15 to 64 ± 11 beats/min; and systolic BP decreased from 158 ± 23 to 140 ± 23 mmHg. The same investigators evaluated changes in plasma and urinary catecholamines in 41 adult patients undergoing vascular surgery.[16] When compared to patients receiving dexmedetomidine, plasma norepinephrine concentrations were 2-3 times higher at the time of tracheal extubation and at 60 minutes after arrival in the post-anesthesia care unit in the control group. Urinary normetanephrine levels increased significantly in the placebo group, while no change was noted in patients receiving dexmedetomidine. A similar sympatholytic effect has been demonstrated following the intraoperative administration of dexmedetomidine to pediatric patients undergoing cardiopulmonary bypass and surgery for congenital heart disease.[17]

Given that autonomic dysfunction with hyperactivity of the sympathetic nervous system may result in perioperative problems in patients with FD, there is sound physiologic rationale for the use of an agent like dexmedetomidine that effectively blunts this response.[18] Dexmedetomidine has been used effectively to control the sympathetic nervous system in other disorders of autonomic dysfunction including withdrawal from alcohol as well as iatrogenic opiate or benzodiazepine use.[19-24] Anecdotal experience has also demonstrated the efficacy of dexmedetomidine to treat paroxysmal autonomic instability with dystonia (PAID). PAID, sometimes referred to as "sympathetic storms" or "dysautonomia," is most often seen in patients with traumatic brain injury, tumor, and acute hydrocephalus.[25] The tachycardia, hypertension, hyperprexia, tachypenea, and diaphoresis seen in PAID patients may be due to a loss of inhibitory input to sympathetic feedback loops.[24] Goddeau et al reported their experience with a 38-year-old patient suffering from PAID after traumatic brain injury, who did not respond to the standard treatment including morphine, fentanyl, labetalol, lorazepam, metoprolol and clonidine. Following the institution of a dexmedetomidine infusion which was titrated to 0.7 μg/kg/hr and continued for 72 hours, all other medications were able to be discontinued and the PAID was well controlled.

There is additional anecdotal experience with the use of dexmedetomidine in patients with FD (Table 1).[26-28] These cases demonstrate the potential utility of using dexmedetomidine as part of a balanced anesthetic technique during intraoperative care. In the first two cases, the dexmedetomidine was discontinued intraoperatively while Koshibe and Lee continued the infusion at a decreased dose of 0.2μg/kg/hr into the recovery phase until the PCA device was started. In our patient, a bolus dose of dexmedetomidine (0.4μg/kg) effectively controlled the postoperative hypertension, tachycardia, and agitation. Our patient's agitation and hemodynamic status was not affected by the use

Table 1: Anecdotal experience with dexmedetomidine in patients with familial dysautonomia

Author and reference	Patient demographics	Dexmedetomidine dosing	Description of outcome
Abulhasan Y et al.[26]	10-month-old girl for laparoscopic gastrostomy tube insertion.	Maintenance anesthesia included propofol (100-150 µg/kg/min) and dexmedetomidine administered as a bolus dose of 0.5 µg/kg followed by an infusion of 0.7 µg/kg/hr.	No hemodynamic changes during surgical manipulation. Infusions of propofol and dexmedetomidine discontinued at the completion of the surgical procedure. One episode of hypertension in the PACU related to pain. Resolved with morphine.
Gurbuxani G et al.[27]	16-year old male undergoing renal transplant surgery	Dexmedetomidine infusion was started at 0.1 µg/kg/hr along with remifentanil 0.05 µg/kg/min for arterial cannula placement. Following induction, dexmedetomidine was continued at 0.2-0.3 µg/kg/hr.	Transient decrease in BO after unclamping the IVC was treated by decreasing dexmedetomidine from 0.3 to 0.2 µg/kg/hr. During emergence, SNP required for BP control. The authors theorized that a large dose of dexmedetomidine may have prevented the BP increase during emergence.
Koshibe G and Lee HT.[28]	27-year old male undergoing renal transplant surgery	Dexmedetomidine infusion at 0.7 µg/kg/hr was started just prior to induction. Induction was intravenous with propofol and succinylcholine followed by midazolam and fentanyl after intubation.	Immediately after intubation the patient's BP rose to 210/130 mmHg. Midazolam and additional divided doses of fentanyl were given with minimal BP change. Nitroprusside infusion (0.2 µg/kg/hr) was started and BP slowly decreased to 150s/100s mmHg. Dexmedetomidine infusion was continued during extubation to decrease stress and the possibility of triggering a dysautonomic crisis.

of narcotics especially with the coexistent breath holding spells. She responded well clinically in the immediate postoperative period and into the next few days of dexmedetomidine therapy. She was easily weaned off dexmedetomidine therapy at the conclusion of her 60 hour course.

In addition to controlling the sympathetic nervous system and potentially preventing the hemodynamic lability, that may occur in patients with FD, dexmedetomidine may also facilitate the emergence process by preventing emergence delirium, decreasing shivering, and potentiation

PACU = post-anesthesia care unit; BP = blood pressure; SNP = sodium nitroprusside

of the opioid analgesia.[6,8,29] The opioid sparing effect of dexmedetomidine may be particularly important in patients with FD. Axelrod et al noted the frequent need for postoperative ventilation with the use of opioids following abdominal surgery in patients with FD.[30]

CONCLUSION

Despite relatively limited anecdotal experience, the physiologic basis of FD and the pharmacologic mechanisms of dexmedetomidine provide a sound physiologic rationale suggesting that it should be considered as a valuable agent in the perioperative management of familial dysautonomia (FD), also known as Riley-Day syndrome.

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