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Remimazolam for sedation during an interventional radiology procedure in a patient with Fontan physiology, septic shock, receiving bilevel positive airway pressure support

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Keypoints

1. Palliation of various single ventricle congenital cardiac lesions, such as tricuspid atresia and hypoplastic left heart syndrome, involve procedures that direct the flow of systemic venous blood return directly into the pulmonary arteries (Fontan or Glenn procedures) by anastomosis of the inferior and/or superior vena cavae to the pulmonary arterial bed.
2. Effective functioning of these palliative procedures requires unobstructed flow, maintenance of preload, adequate contractile function of the single ventricle, and a low-normal pulmonary vascular resistance to allow unimpeded flow of blood through the pulmonary circulation. In this scenario, preservation of spontaneous ventilation is advantageous because negative intrathoracic pressure supports systemic venous return, increasing pulmonary blood flow.
3. Remimazolam is a novel ultra-short-acting benzodiazepine, which like midazolam has sedative, anxiolytic, and amnestic properties. Rapid metabolism by peripheral tissue esterases results in a rapid offset and a limited context-sensitive half-life, which make it a suitable agent by bolus or continuous infusion for procedural sedation with a native airway and spontaneous ventilation.
4. Clinical trials have demonstrated that remimazolam has a favorable adverse-effect profile with a potentially lower incidence of hypotension and respiratory depression than more commonly used agents such as propofol.

Abstract

Palliation of various single ventricle congenital cardiac lesions, such as tricuspid atresia and hypoplastic left heart syndrome, involves procedures that direct the flow of systemic venous blood return directly into the pulmonary arteries (cavo-pulmonary connections), classically known as the Fontan procedure. This circulatory pattern is unique as there is no ventricle to actively pump blood through the lungs. Effective functioning of the novel circuit requires unobstructed flow, maintenance of preload, adequate contractile function of the single ventricle, and a low-normal pulmonary vascular resistance. These components allow unimpeded flow of blood through the pulmonary circulation to the left side of the circulation. Preservation of spontaneous ventilation is advantageous because negative intrathoracic pressure

during inspiration supports systemic venous return and passive pulmonary blood flow. We present a 12-year-old adolescent with Fontan physiology who required procedural sedation for placement of a hemodialysis catheter in the interventional radiology suite. Procedural sedation during IR procedures is discussed, benefits of spontaneous ventilation in Fontan physiology reviewed, and use of remimazolam as the primary agent in these scenarios presented.

Keywords

remimazolam; interventional radiology; Fontan physiology

Introduction

Palliation of various single ventricle congenital cardiac lesions, such as tricuspid atresia and hypoplastic left heart syndrome, involve procedures that direct the flow of systemic venous blood return directly into the pulmonary arteries.[1,2] The first surgical attempts at these procedures included direct anastomosis of the superior vena cava (SVC) to the pulmonary artery by Glenn and Patino in 1954, followed by Fontan and Baudet describing anastomosis of the right atrium to the pulmonary artery using an aortic homograft.[3,4] The surgical approach and variations of these procedures have evolved over time, but the goal remains the same, a separation of the systemic and pulmonary circulations by directing systemic venous return from the superior and inferior vena cava to the pulmonary arteries, leaving the single functioning ventricle to support systemic blood flow. This circulation remains unique because there is no sub-pulmonary ventricle actively pumping blood through the lungs. Effective functioning of these palliative procedures requires unobstructed flow, maintenance of intravascular volume (preload), adequate contractile function of the single ventricle, and a low-normal pulmonary vascular resistance to allow unimpeded flow of blood through the pulmonary circulation. Preservation of spontaneous ventilation may be advantageous because negative intrathoracic pressure during inspiration supports systemic venous return and passive pulmonary blood flow. In contrast, positive-pressure ventilation may increase intrathoracic pressure, reduce venous return, and impair preload.[5-7] Since pulmonary blood flow in the Fontan circulation occurs without a dedicated sub-pulmonary ventricle, anesthetic techniques that avoid myocardial depression, maintain low pulmonary vascular resistance, and preserve effective spontaneous ventilation may help support hemodynamic stability. We present a 12-year-old adolescent female with Fontan physiology who presented to the interventional radiology (IR) suite for placement of a hemodialysis catheter to treat anuric renal failure secondary to shock. Procedural sedation during IR procedures is discussed, benefits of spontaneous ventilation in Fontan physiology reviewed, and use of remimazolam as the primary agent in these scenarios presented.

Case report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital. Written consent was obtained for the use of deidentified patient information for publication.

The patient was a 12-year-old, 102.1-kg adolescent with complex congenital heart disease, including double-outlet right ventricle, ventricular septal defect, ventricular inversion, hypoplastic aortic arch, and Ebstein anomaly. She had previously undergone hybrid palliation followed by a comprehensive stage II reconstruction, including placement of a bidirectional Glenn shunt at age 1 and Fontan completion at 3 years of age. Her subsequent course was complicated by Fontan-associated hepatic dysfunction. Her baseline oxygen saturation was approximately 90% while breathing room air during the day, and she received supplemental oxygen at 1 L/min by nasal cannula overnight. Her most recent echocardiogram demonstrated normal atrial chamber sizes. The mitral valve had normal-appearing leaflets with trace regurgitation, while the tricuspid valve was Ebsteinoid with trace

regurgitation. The aortic valve was trileaflet with mild regurgitation. The single functional ventricle was a morphologic right ventricle with normal systolic function and no evidence of hypertrophy. The sinuses of Valsalva and aortic root were mildly enlarged. Her medical history was additionally notable for a thoracic aortic dissection with an intramural hematoma involving the descending aorta, status post stent placement, requiring chronic anticoagulation. A bedside echocardiogram during the current hospitalization demonstrated a patent Fontan pathway with appropriate ventricular function and a patent aortic stent. Additional comorbid conditions included precursor B-cell acute lymphoblastic leukemia in maintenance therapy, severe combined immunodeficiency, hypoxic-ischemic encephalopathy, epilepsy treated with levetiracetam, obstructive sleep apnea, obesity (body mass index, 40.9 kg/m^2), diabetes mellitus, chronic kidney disease, scoliosis, ADHD, and anxiety. As treatment for her ongoing cardiac dysfunction, she had recently been started on sacubitril/valsartan (Entresto).

The patient presented to the emergency department with severe hypotension, hypoxemia, and black, tarry stools concerning for melena. Her initial temperature was 37.8°C (100.0°F), heart rate was 116 beats/min, respiratory rate was 24 breaths/min, blood pressure was 87/35 mmHg, and oxygen saturation was 74% while receiving oxygen at 3 L/min via a Venturi mask. Despite the hypoxemia, her respiratory effort was normal, without any documented respiratory distress. She appeared pale, with a capillary refill time of 2-3 seconds, but remained at her baseline mental status. Intravenous fluid resuscitation was initiated but did not produce an appreciable improvement in her blood pressure. Point-of-care analysis demonstrated a hemoglobin concentration of 8.0 g/dL, while a complete blood count demonstrated a hemoglobin concentration of 7.3 g/dL, decreased from 11.9 g/dL approximately one week earlier, and a platelet count of 23 x 10^3/μL. Fecal occult blood testing was positive. Given the concern for gastrointestinal hemorrhage, packed red blood cells were ordered. Laboratory evaluation also demonstrated an increase in serum creatinine to 4.08 mg/dL from a baseline of approximately 0.4 mg/dL. Venous blood gas analysis and serum lactate were reassuring. She was admitted to the pediatric intensive care unit for management of septic shock with a hemorrhagic component and severe acute kidney injury. Empiric antimicrobial therapy was initiated with cefepime, linezolid, and metronidazole. Initial blood cultures remained negative, and no bloodstream or body-fluid source was identified. She initially required norepinephrine and epinephrine infusions for fluid-refractory hypotension. Because of persistent severe hypotension, hemodynamic support was escalated to vasopressin and subsequently angiotensin II.[8] Over the first 72 hours of hospitalization, evidence of gastrointestinal bleeding ceased and her hemodynamics stabilized, allowing vasoactive support to be weaned and discontinued before the IR procedure.

Following initial in-hospital resuscitation, Nephrology was consulted for management of her severe acute-on-chronic kidney injury, and placement of a hemodialysis catheter was required to facilitate renal replacement therapy. Before the procedure, laboratory evaluation demonstrated a blood urea nitrogen concentration of 71 mg/dL, serum creatinine of 1.19 mg/dL, and mild hyperphosphatemia with serum phosphorus concentration of 5.6 mg/dL. Her metabolic acidosis had improved, with an increase in serum bicarbonate from 13 to 20 mEq/L. Her hemoglobin concentration was 11 g/dL. Persistent thrombocytopenia was present, with a platelet count of 32 x 10^3/μL. Chronic anticoagulation was held until after completion of the procedure. On hospital day 4, the patient was transported to the IR suite for placement of a hemodialysis catheter under ultrasound guidance. Upon arrival, she was positioned supine with her arms tucked at her side and her head and neck maintained in alignment with the spine: a field-avoidance configuration was used. She was classified as American Society of Anesthesiologists' (ASA) physical status IV. The planned anesthetic technique was intravenous monitored anesthesia care

with procedural sedation and conversion to general anesthesia if necessary. The goal was to maintain spontaneous ventilation to facilitate flow through the Fontan circulation. Standard ASA monitors, including capnography, were applied. She remained spontaneously ventilating while receiving oxygen through a high-flow nasal cannula at 15 L/min with an initial inspired oxygen concentration of 40%. Intravenous midazolam (2 mg) and ketamine (20 mg) were administered, followed by a remimazolam loading dose (5 mg) over 2-3 minutes. Following the remimazolam bolus dose, a remimazolam infusion (2.5 mg/mL of 0.9% sodium chloride) was initiated at 5 μg/kg/min and titrated from 5-10 μg/kg/min to maintain the needed level of sedation. Local infiltration was initiated with 1% lidocaine, and a hemodialysis catheter was placed in the right internal jugular vein under ultrasound guidance. The patient maintained spontaneous ventilation throughout the procedure without airway obstruction or need for advanced airway instrumentation. Her heart rate ranged from 117 to 128 beats/min, blood pressure from 151/64 to 155/66 mmHg, oxygen saturation from 89% to 96%, and end-tidal carbon dioxide concentration from 31 to 32 mmHg. Given her thrombocytopenia, she received a 258-mL platelet transfusion during the procedure. Her platelet counts initially increased to 41 x 10^3/μL before decreasing to 29 x 10^3/μL several hours later. The hemodialysis catheter was successfully placed without documented procedural or anesthetic complications during the 30-minute procedure. The total cumulative dose of remimazolam (loading dose and 21-minute infusion) was approximately 0.2 mg/kg. The patient was returned to the pediatric intensive care unit, breathing spontaneously through a high-flow nasal cannula at 15 L/min with an oxygen saturation of 90%, consistent with her baseline. Continuous renal replacement therapy with dialysis (CRRT-D) was initiated the day after the procedure. This was subsequently transitioned to intermittent RRT and then discontinued as her renal function and fluid status improved after a total of 10-12 days. A *Clostridioides difficile* infection was subsequently identified and treated with a 10-day course of fidaxomicin, with resolution of symptoms. Although during this time respiratory support was escalated to BiPAP because of decreasing lung volumes on serial chest radiographs, support was later weaned back to HFNC and then to her baseline of room air during the day and 1 L/min by nasal cannula overnight as fluid status improved. Following continued clinical improvement, she was transferred from the pediatric intensive care unit to the inpatient ward on hospital day 21. She was discharged home on hospital day 27, after a 26-day hospitalization, with outpatient cardiology follow-up. At discharge, sacubitril/valsartan was not restarted, home medication of carvedilol was decreased to 25 mg twice daily, and oral furosemide and spironolactone were initiated.

Discussion

In pediatric-aged patients, procedural sedation is frequently required to facilitate diagnostic and therapeutic procedures outside the operating room as a means of limiting anxiety and providing a motionless patient to allow for successful completion of the procedure.[9] Depending on the training and experience of the provider as well as the clinical scenario, commonly used agents include benzodiazepines (midazolam), ketamine, opioids (fentanyl), dexmedetomidine, and propofol, either alone or in combination.[10] However, sedation occurs along a continuum, and at times, there may be unintended progression to a deeper level of sedation which can result in airway obstruction, apnea, hypoventilation, hypoxemia, or hemodynamic instability. Data from the Pediatric Sedation Research Consortium have demonstrated that serious adverse outcomes are uncommon when pediatric sedation is delivered through an organized system, although airway and respiratory events requiring intervention still occur.[11,12] These findings emphasize the importance of continuous physiologic monitoring, the presence of personnel capable of airway rescue, and immediate availability of resuscitation equipment in accordance with guidelines set by the American Academy of Pediatrics and the

American Society of Anesthesiologists. These considerations are particularly relevant in clinical scenarios like our current patient because of the presence of significant comorbid conditions including obesity, obstructive sleep apnea, baseline hypoxemia, acute respiratory insufficiency, Fontan physiology, and recent septic and hemorrhagic shock. These conditions have been shown to significantly increase the incidence of adverse effects during procedural sedation.[13,14]

In our patient, given the impact of positive pressure ventilation on Fontan physiology, our intent was to provide procedural sedation while maintaining spontaneous ventilation and preserving the option to convert to general anesthesia with endotracheal intubation and controlled ventilation if necessary. In the Fontan circulation, pulmonary blood flow is passive and depends on a low-resistance pressure gradient from the systemic veins through the pulmonary vascular bed. Consequently, maintaining intravascular volume, ventricular contractility, sinus rhythm, and a low pulmonary vascular resistance (PVR) are essential.[5,7,15,16] Hypoxemia, hypercarbia, acidosis, pain or procedural stress, hypothermia, atelectasis, and excessive lung inflation may increase PVR and reduce pulmonary blood flow.[5,15,16] Spontaneous ventilation enhances systemic venous return and ventricular preload by maintaining a negative intrathoracic pressure, whereas positive-pressure ventilation may reduce venous return and cardiac output.[5,7] In a recent prospective crossover study of 35 anesthetized children with Glenn or Fontan connections, cardiac index was 0.6 L/min/m^2 higher during spontaneous ventilation than during mechanical ventilation, an effect attributed primarily to improved ventricular preload.[17] This benefit depends on unobstructed ventilation because airway obstruction or hypoventilation may cause hypoxemia and hypercarbia, thereby increasing PVR. In our patient, a remimazolam-based sedation regimen with high-flow nasal cannula support allowed for placement of the dialysis catheter while preserving spontaneous ventilation, avoiding airway instrumentation, and maintaining oxygen saturation near her baseline without hemodynamic instability.

Remimazolam is a novel, ultra-short-acting benzodiazepine that, like midazolam, provides sedation, anxiolysis, and amnesia through enhancement of gamma-aminobutyric acid type A (GABA-A) receptor activity.[18] It is rapidly hydrolyzed by carboxylesterase-1 tissue esterases to a pharmacologically inactive metabolite, resulting in rapid clearance and a limited context-sensitive half-time. In 2020, remimazolam received FDA approval for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less. Randomized trials in adults have demonstrated effective sedation during short procedures, including colonoscopy and bronchoscopy, with a rapid onset and faster recovery than midazolam-based comparators.[19,20] Remimazolam has also been evaluated for the induction and maintenance of general anesthesia in adults, with a phase IIb/III trial demonstrating non-inferiority to propofol and a lower incidence of hypotension.[21]

Although pediatric use remains off-label, clinical experience with the use of remimazolam as a primary agent or adjunct for procedural sedation or general anesthesia continues to expand.[22,23] Similar to the adult population, pharmacokinetic data from pediatric-aged patients demonstrate a rapid clearance and a short context-sensitive half-life of approximately 17 minutes following a 4-hour infusion.[24] In our patient, the rapid titratability and limited context-sensitive half-time of remimazolam made it an attractive component of a multimodal technique for a short procedure in a child at high risk for hemodynamic and respiratory compromise. Remimazolam, combined with a bolus dose of ketamine, provided adequate conditions for dialysis catheter placement while spontaneous ventilation was maintained, airway instrumentation was avoided, and oxygen saturation remained near baseline. An additional advantage of remimazolam is that if adverse effects occur, its effects can also be antagonized with flumazenil.[18] Because adjunctive medications and high-flow nasal oxygen were used, the clinical course

cannot be attributed to remimazolam alone; rather, this case demonstrates the feasibility of remimazolam-based procedural sedation in a carefully monitored setting with appropriate non-invasive airway support and immediate airway-rescue capabilities.

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