Anesthetic Management of an Adolescent With Marfan Syndrome During Anterior Spinal Fusion

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Abstract

Marfan syndrome (MFS) is an autosomal dominant disorder resulting from a mutation of the gene encoding fibrillin-1 (FBN1) on chromosome 15. Fibrillin-1 is a matrix glycoprotein essential for the formation of microfibrils that regulate the formation and repair of connective tissue throughout the body. This primary cellular defect results in a multisystem disorder of connective tissue. Given the multisystem involvement of MFS, anesthetic care is frequently required during surgical or orthopedic procedures. We present a 15-year-old adolescent who required anesthetic care during spinal fusion. The perioperative implications of MFS are reviewed and options for anesthetic care presented.

Keywords: Spinal fusion; Kyphoscoliosis; Marfan syndrome; Anticoagulation

Introduction

Marfan syndrome (MFS) is a systemic disorder resulting from a primary disorder of connective tissue, first described by the Parisian pediatrician, Antonie-Bernard Marfan in 1896 [1, 2]. Its incidence is approximately 1 in 10,000 - 20,000 individuals, and it is inherited as an autosomal dominant trait, although at least 25% of cases result from a new mutation in the *FBN1* gene (see below). The clinical diagnosis is based on the revised Ghent criteria and can be confirmed by genetic testing [3]. The

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primary organ systems involved include the heart, aorta, eye, musculoskeletal, skin, lung, and central nervous system [3]. Involvement of the heart and aorta are recognized as the major cause of morbidity and mortality in patients with MFS. Dilation of the ascending aorta occurs in 77% of affected individuals, with progression to dissection in 14% of patients [4].

The primary cellular defect of MFS is a mutation of the gene encoding fibrillin-1 (FBN1) on chromosome 15 (15q21.1) [5]. Fibrillin-1 is a matrix glycoprotein essential for the formation of microfibrils that regulate the formation and repair of connective tissue throughout the body. These microfibrils are also integral to the normal control and function of growth factors including tissue growth factor-beta (TGF-β), which are responsible for the development and repair of connective tissue. Fibrillin-1 regulates TGF-β which activates metalloproteinases (MMPs). The combination of structural microfibril matrix abnormalities and dysregulation of matrix homeostasis mediated by excess TGF-β and overexpression of MMPs is responsible for the phenotypic features of MFS in various organ systems [6, 7].

The imbalance between MMPs and tissue inhibitors of MMPs (TIMPs) damages the elastin structure, leading to loss of vascular smooth muscle cells, with the associated clinical manifestations involving the aorta and heart. Given the multisystem involvement of MFS, anesthetic care is frequently required during surgical or orthopedic procedures [8]. We present a 15-year-old adolescent who required anesthetic care during spinal fusion. The perioperative implications of MFS are presented, previous reports of anesthetic care reviewed, and options for perioperative care discussed.

Case Report

Institutional Review Board approval is not required at Nationwide Children's Hospital (Columbus, Ohio) for the presentation of single case reports. The patient was a 15-year-old, 54 kg adolescent who presented for posterior spinal fusion for the treatment of thoracolumbar kyphoscoliosis. Her past medical history was significant for MFS, psychiatric disorder with a history of aggressive behavior, and attention deficit disorder. Her past surgical history included mechanical aortic valve replacement 3 years prior to the current surgery. Aortic valve sparing aortic root replacement and mitral valve repair were performed 6 years prior to surgery. Her medication regimen included warfarin 5 mg once a day, aspirin 81 mg once a day

and losartan 25 mg once a day.

Warfarin and aspirin were discontinued 4 days prior to surgery and full anticoagulation provided by a continuous heparin infusion. Echocardiogram 5 months prior to the procedure demonstrated mitral valve prolapse with mild regurgitation and normal systolic function. The heparin infusion rate was based on laboratory parameters (partial thromboplastin time (PTT) and anti-factor Xa assay). The patient was held *nil per os* for 8 h. The heparin infusion was discontinued 4 h prior to the surgery; however, the PTT remained elevated at 60 s, so the surgical procedure was delayed for 1 hour and a repeat PTT was obtained (44 s).

The patient was premedicated with intravenous midazolam (2 mg) through a pre-existing peripheral intravenous cannula, and transported to the operating room, where routine American Society of Anesthesiologists' monitors were placed. Following preoxygenation with 100% oxygen, anesthesia was induced with propofol (130 mg), lidocaine (60 mg), and sufentanil (20 µg). Bag-valve-mask ventilation was provided without difficulty. Rocuronium (50 mg) was administered to facilitate endotracheal intubation. Direct laryngoscopy was performed with a Miller 2 blade and revealed a Cormack-Lehane Grade 1 view. A 7.0 mm cuffed endotracheal tube was placed on the first attempt. Two 16 gauge intravenous cannulas were placed. A 20 gauge arterial cannula was placed in the left radial artery. Neurophysiological monitoring, including motor evoked potentials (MEP) and somatosensory evoked potentials (SSEPs) was performed.

Following our usual practice to allow for neurophysiological monitoring during spinal surgery, anesthesia was maintained with desflurane titrated to maintain the bispectral index (BIS) at 50 - 60 and a sufentanil infusion of 0.1 - 0.3 µg/kg/h to maintain the mean arterial pressure at 55 - 65 mm Hg [9]. An esmolol infusion (25 - 30 µg/kg/min) was administered to maintain the heart rate at the baseline rate of 60 - 80 beats/min and a lidocaine infusion (30 µg/kg/min) was administered to prevent arrhythmias and to provide analgesia. The patient was placed in the right lateral decubitus position. The surgical procedure included an anterior arthrodesis of the thoracic and lumbar spine (T11-L4) through an anterior thoracoabdominal incision. The surgical duration was 400 min. Total blood loss was estimated at 750 mL and urine output was 325 mL. Total fluids included 1,774 mL of isotonic crystalloid, 500 mL of 5% albumin, and one unit of packed red blood cells.

During wound closure, the sufentanil infusion was discontinued. Acetaminophen (1,000 mg) and hydromorphone (0.5 mg) were administered to provide postoperative analgesia. After completion of the surgical procedure and prior to tracheal extubation, bilateral ultrasound-guided, erector spinae blocks were performed with 0.25% ropivacaine (20 mL) with epinephrine (1:200,000) and preservative-free dexamethasone (4 mg). Following completion of the blocks, the patient was turned supine and her trachea was extubated in the operating room. She was transported to the cardiothoracic intensive care unit (CTICU). Postoperative pain control in the CTICU was provided with hydromorphone delivered via a patient controlled analgesia device. Warfarin was restarted on postoperative day (POD) 1. Enoxaparin was administered from POD 1 to 4. The remainder of her postoperative course was uncompli-

cated and she was discharged on POD 6.

Discussion

MFS is a well described, autosomal dominant connective tissue disease caused by mutation of the *FBN1* gene. The diagnosed is based on the revised Ghent nosology established in 2010 [3]. Aortic diameter at the sinuses of Valsalva (z value ≥ 2), aortic root dissection, ectopia lentis, and the *FBN1* mutation are the most important factors for diagnosis [3]. Effective perioperative care begins with a thorough preoperative evaluation, with identification of anatomical and end-organ effects of MFS, as well as adverse effects or implications related to therapeutic interventions, such as the long-term anticoagulation required in our patient. Of primary concern to anesthesia providers is the potential for difficult endotracheal intubation related to a high arched palate and temporomandibular joint (TMJ) dislocation [10-12]. A significant percentage of patients with MFS have a high arched palate (59%). TMJ involvement is also common, with symptoms of TMJ dysfunction noted in 52% of patients with MFS, of whom 35% had previously received medical treatment, and 24% had symptoms of subluxation [4, 11]. Given these concerns, the appropriate equipment for dealing with a difficult airway, including an indirect laryngoscopy device, should be readily available prior to anesthetic induction [13, 14]. If there are concerns, general anesthesia can be induced by the incremental inhalation of sevoflurane in 100% oxygen with the maintenance of spontaneous ventilation until effective bag-valve-mask ventilation is demonstrated. Alternatively, as in our patient, intravenous induction can be achieved with propofol, and effective bag-valve-mask ventilation can be followed by the administration of a neuromuscular blocking agent.

Airway involvement with craniofacial abnormalities and laxity of upper airway musculature results in a high prevalence of obstructive sleep apnea (OSA) in patients with MFS, even in the absence of obesity. Craniofacial and upper airway skeletal muscle involvement results in increased nasal airway resistance and upper airway collapse [15, 16]. Given the residual effects of opioids and neuromuscular blocking agents on respiratory function, postoperative monitoring may be indicated, especially when ongoing pain management requires the use of opioids [17].

In addition to airway abnormalities, respiratory and pulmonary involvement may predispose to barotrauma due to blebs or bullae. The frequency of spontaneous pneumothorax has been reported to be as high as 4-15% in patients with MFS [2, 18]. Apical blebs or bullae significantly increase the risk of spontaneous pneumothorax. When there are concerns noted on a preoperative chest radiograph, computed tomography may help in risk stratification. Additionally, chest wall and vertebral bony abnormalities (scoliosis or pectus excavatum) may impact respiratory function. Progressive scoliosis is a well-known cause of pulmonary dysfunction. Scoliosis with a curve greater than 65, 100, and 120 degrees may result in restrictive lung disease noted only on pulmonary function testing, symptomatic lung disease with a clinical impact, and alveolar hypoventilation, respectively [19, 20].

Patients with MFS and scoliosis or pectus excavatum may have marked reductions in total lung capacity, forced vital capacity, and forced expiratory volume over 1 s (FEV_1). Pulmonary function values calculated by body height underestimate true values in patients with MFS because of long-bone overgrowth. Expected values calculated by normalized or sitting height are suggested to give a better evaluation of true pulmonary function [21]. Given these concerns, intraoperative strategies to minimize barotrauma may be indicated, including the use of lower tidal volumes, careful monitoring or peak inflating pressure, prolongation of the inspiratory time, and pressure-controlled ventilation with monitoring of exhaled tidal volume. If alterations in compliance or resistance are noted, the potential for a pneumothorax as the etiology must be considered.

Postoperatively, severe kyphoscoliosis related to neuromuscular disease, as well as OSA and primary respiratory involvement, may predispose to respiratory insufficiency or failure. Patients who have abnormal results on their pulmonary function test, particularly a forced vital capacity less than 30%, or those who have hypercapnia preoperatively have been shown to have a higher need for postoperative ventilation [22]. Preoperative optimization of pulmonary function is suggested, including the aggressive treatment of respiratory infections and instructions regarding the use of postoperative incentive spirometry. Non-invasive techniques of respiratory support, such as bilevel positive airway pressure (BiPAP), may facilitate postoperative tracheal extubation and avoid postoperative respiratory insufficiency or failure in patients with pre-existing pulmonary dysfunction [23, 24].

As noted in our patient, the cardiovascular system is frequently affected in patients with MFS, including aortic and pulmonary artery dilation, valvular regurgitation, left ventricular dysfunction, and arrhythmias. MVP is the most common cause of severe mitral valve regurgitation, as upregulation of TGF-β results in myxomatous changes of the atrioventricular valves [25]. This results in elongation and thickening of atrioventricular valve leaflets. By 30 years of age, the Weibull cumulative distribution has been reported to be 42.6% for MVP, 56.5% for MVR of any degree, 6.7% for severe MVR, and 0.9% for MV endocarditis in patients with MFS [26]. In children with early onset of severe MFS, mitral valve dysfunction, which can lead to pulmonary hypertension and congestive heart failure, is the leading cause of death in infancy. Tricuspid valve regurgitation and prolapse can also occur, although surgery is rarely required [27]. Aortic valve regurgitation can occur as well, but it generally occurs in the second and third decade of life, related to progressive aortic root dilation.

Aortic root dilation is the most common cardiovascular manifestation of MFS, occurring in 60% of affected individuals. Aortic root rupture and dissection remain the most life-threatening events in patients with MFS. The aorta dilates most between 6 to 14 years of age [28]. Management may include both medical and surgical management options. Medical therapy includes a combination of β-adrenergic antagonists and angiotensin receptor blockers (ARB). Beta-adrenergic blockade reduces heart rate, blood pressure, and aortic root dilation [29]. The target heart rate is less than 60 - 70 beats per minutes at rest [30]. Intraoperatively, esmolol may be used to provide rapid and precise heart rate control. ARBs regulate excessive TGF-β signaling, which may play an etiologic role in aortic root dilation [31].

Ascending aorta root replacement is the only way to prevent fatal events including dissection and rupture. Elective surgery is recommended when the maximum aortic root diameter is greater than 5.0 - 5.5 cm in adult patients. If the patients have a family history of aortic rupture, or increase in aortic diameter exceeding 1 cm/year, earlier surgical intervention is recommended. Various surgical procedures have been offered, including various valve sparing procedures which preserve the native aortic valve and eliminate the need for long-term anticoagulation [32-34]. When mechanical valve replacement is performed, long-term anticoagulation with coumadin is required.

Guidelines for perioperative anticoagulation therapy have been published by the American Heart Association and the American College of Cardiology [35]. As in our patient, coumadin or other oral anticoagulation agents are stopped 3 - 4 days prior to surgery, and full anticoagulation started with heparin (unfractionated or low molecular weight) once the international normalized ratio (INR) falls below the therapeutic threshold. Intravenous unfractionated heparin is stopped 4 - 6 h prior to surgery and subcutaneous low molecular heparin is stopped 12 h prior to surgery, to allow return of coagulation function to normal. Anticoagulation is restarted as soon as the postoperative bleeding risk allows, typically 12 to 24 h after surgery.

In addition to valvular dysfunction and aortic root dilation, ventricular arrhythmias may occur in up to 21% of patients with MFS, with one report suggesting that this was the cause of death in 4% of patients [36]. Non-sustained ventricular tachycardia was also noted in 40% of patients. Microfibril abnormalities in the matrix of the myocardium result in arrhythmogenesis and may affect conduction [37]. Given these concerns, a preoperative 12-lead ECG and echocardiogram are suggested. A more thorough workup such as a Holter monitor may be indicated in patients with symptoms.

Ocular involvement, including ectopia lentis, is common in MFS and may predispose to perioperative visual loss (POVL) during spine surgery. Additional ocular involvement may include thinning of the cornea, early onset of cataracts, glaucoma, strabismus, and retinal detachment. Although POVL is rare, its impact on the quality of life is significant, and spinal surgery represents a high risk population with an incidence of POVL ranging from 0.017% to 0.1% [38]. Ischemic injury to the optic nerve due to venous congestion is the most common cause of POVL following spinal surgery. Symptoms present immediately after the surgery and are typically bilateral. Risk factors include anemia, hypotension, blood loss, prolonged surgical times, large fluid requirements, male gender and obesity [39, 40]. Prevention should remain the primary focus, with routine position checks to ensure that there is no direct pressure on the eyes or orbits. Others have suggested the use of colloid instead of crystalloid as well as avoidance of hypotension, anemia, and hypovolemia. A staged procedure should be considered if a long surgery is anticipated.

Finally, intraoperative monitoring of spinal cord function with somatosensory-evoked potentials (SSEPs) and motor-evoked potentials (MEPs) further impacts anesthetic manage-

ment during PSF [41]. Both inhaled and intravenous anesthetic agents may depress SSEP and MEP signal attainment [42]. Our general practice includes the use of a low dose of an inhalational anesthetic agent combined with the infusion of a potent opioid (sufentanil or remifentanil) [9]. When inhalational anesthetic agents are used, it is generally recommended to maintain end-tidal concentrations levels at or below 0.5 MAC (minimum alveolar concentration) to allow for adequate MEP monitoring. These agents provide an effective intraoperative anesthetic while allowing for neurophysiological monitoring and providing a rapid emergence at the conclusion of the case.

In summary, we present the perioperative management of an adolescent with MFS for spinal fusion. As the primary defect affects fibrillin-1, a matrix glycoprotein essential for the formation and repair of connective tissue, multisystem involvement is present. Progressive skeletal deformities may require orthopedic procedures such as spinal fusion. Most importantly, the cardiovascular system may be involved with valvular regurgitation, aortic root dilation, and arrhythmias. Additional comorbid concerns include airway involvement (difficult intubation, sleep disordered breathing), respiratory involvement (risk of barotrauma), and ocular involvement. The preoperative evaluation is essential to identify anatomical and end-organ effects of MFS, as well as implications of therapeutic interventions, such as long-term anticoagulation.

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Conflict of Interest

The authors do not have conflict of interest.

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