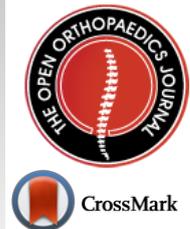


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## REVIEW ARTICLE

### Anesthesia for Patients with Juvenile Idiopathic Arthritis Current Practice: A Review

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#### Abstract:

Juvenile Idiopathic Arthritis is one of the most common chronic diseases in children. The disease affects one or multiple joints. Additionally, systemic involvement can be present either due to the condition itself or due to pharmacologic side effects resulting from treatment. This article reviews different aspects of perioperative management of patients with Juvenile Idiopathic Arthritis. It outlines the risks and difficulties secondary to articular damage, and also pharmacologic treatment strategies interfering with the anesthetic plan.

**Keywords:** Juvenile idiopathic arthritis, Anesthesia, Juvenile arthritis perioperative management, Perioperative care, Juvenile rheumatoid arthritis, Pharmacologic.

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## 1. INTRODUCTION

With a reported incidence of 11.9 per 100,000 persons/year [1], Juvenile Idiopathic Arthritis (JIA) is one of the most common chronic diseases in children. The common factor in JIA is persistent arthritis in at least one joint with an onset before the age of 16. JIA is a heterogeneous disease, prevalent more in females, that can be divided into three subgroups: oligoarticular, polyarticular and systemic. Oligoarticular disease is the most common, followed by polyarticular and systemic disease [2]. Oligoarticular disease can progress to polyarticular disease in 11% of cases [3]. Systemic Juvenile Idiopathic Arthritis is a subtype of JIA that is characterized by fever, arthritis and one of the following: rash, generalized lymphadenopathy, hepatomegaly and/or splenomegaly, and serositis. Knee and hip joints are most often affected and often require surgical intervention as the disease progresses. In this review, we will discuss anesthetic considerations pertaining to this patient population.

## 2. DISEASE MANIFESTATION

Evaluating the musculoskeletal and non-musculoskeletal manifestations of the disease is necessary during the preoperative period [4]. Particular attention should be given to the cervical spine, temporomandibular and cricoarytenoid joints. Surveying systemic involvement of the heart, respiratory system and clotting cascade is warranted, as is reviewing the

patient's current pharmacologic therapy, as these factors may interfere with anesthesia. Pain management of patients with systemic Juvenile Idiopathic Arthritis may be challenging.

### 2.1. Risks and Difficulties Secondary to Articular Damage

Articular involvement extends beyond the knee and hip joints. Involvement of the cervical spine, temporomandibular joint, and the cricoarytenoid joints is seen in Juvenile Idiopathic Arthritis and has significant implications for airway management.

#### 2.1.1. Cervical Spine

Evaluation for cervical spine instability clinically, and if necessary, by further imaging should be done prior to any surgical procedure. Cervical spine films with flexion extension lateral views should be obtained and MRI should be performed if needed. Specific cervical pathology such as myelopathy, basilar invagination of C1-2 or sub-axial instability with space available for the cord of no more than 13 mm indicates that evaluation by a spine surgeon would be prudent [4, 5].

#### 2.1.2. Temporomandibular Joint

Temporomandibular Joint (TMJ) involvement is common in children with Juvenile Idiopathic Arthritis and is difficult to evaluate clinically. Due to difficulty in diagnosing arthritis of the TMJ, the prevalence varies widely, with a reported incidence ranging from 11% to 87% [6]. These patients may report pain, stiffness, popping, and clicking of the joint, though

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visible joint swelling is usually absent on examination. While clinical tests evaluating TMJ involvement have low sensitivity and specificity, arthritis is best diagnosed with MRI.

Patients with TMJ involvement are at risk for asymmetrical facial growth, which affects airway management. Unilateral TMJ involvement can lead to facial asymmetry, whereas bilateral involvement can lead to mandibular retrognathia with counterclockwise rotation [6]. Hsieh *et al.* found that patients with Juvenile Idiopathic Arthritis and either unilateral or bilateral TMJ involvement had a more retrognathic mandible and retruded chin, steeper occlusal plane and mandibular plane angles and a more hyperdivergent pattern than those without TMJ involvement [7]. Temporomandibular joint ankylosis affects female and male patients equally and primarily occurs in the first decade of life [8]. Deformities of the TMJ result in impaired and painful mouth opening as well as potential difficulties in airway management. Mandibular hypoplasia can lead to difficulty with endotracheal tube placement. Early diagnosis and treatment are key in order to minimize deleterious effects. Facial asymmetry with dysfunction and pain may also require surgical intervention.

### 2.1.3. Cricoarytenoid Joints

The cricoarytenoid joints are small diarthrodial joints. When inflamed, hoarseness ensues, and, on rare occasions, can progress to fatal airway obstruction [5]. More common in adult patients with Rheumatoid Arthritis (RA), a few cases of cricoarytenoid arthritis in children with Juvenile Idiopathic Arthritis have been described [9].

### 2.1.4. Knee and Hip Joints

Unilateral or bilateral articular involvement of the hip and/or knee joints may necessitate total joint arthroplasty to relieve pain and improve function. Radiographs are commonly used for joint evaluation. In some cases, CT scans or MRI imaging might be needed for further surgical evaluation. Hemke *et al.* confirmed the feasibility of non-contrast open-bore MRI in children. The imaging was performed without sedation but with a parent sitting with their child as young as five years of age. In MRI, active and inactive disease states can be identified [10].

Total joint arthroplasty can be unilateral or bilateral arthroplasty that is either performed staged or simultaneously, meaning under two different or the same anesthesia. The advantages of simultaneous bilateral arthroplasty include a shortened hospital length of stay and rehabilitation period. Deep venous thrombosis, pulmonary embolism, cardiac events, and mortality have been studied to determine if any of the above complications are significantly increased with simultaneous or staged bilateral procedures. A meta-analysis by Restrepo *et al.* identified a higher risk of cardiac complications (odds ratio = 2.49) and mortality (odds ratio = 2.2) in patients undergoing simultaneous bilateral arthroplasty [11]. Most complications arise in the first 24 hours after surgery. Yoon *et al.* included ASA physical status classification in determining who is at higher risk and identified that ASA 3 and 4 had a significantly increased risk for systemic complications when undergoing simultaneous bilateral knee arthroplasty [12].

Patients with Juvenile Idiopathic Arthritis are typically younger than the typical patient population undergoing total joint arthroplasty, but due to the systemic disease involvement, the risk for complications remains. During simultaneous bilateral procedures, blood loss needs to be strictly evaluated and appropriate measures should be taken. Before continuing to the second side, we encourage a discussion about the hemodynamic stability of the patient between anesthesiology and surgical team.

## 2.2. Systemic Disease of Interest to Anesthesiologists

Thorough systemic evaluation focusing on the cardiopulmonary systems and clotting cascade should be performed in the perioperative period in patients with JIA, as cardiovascular involvement is a major source of morbidity and mortality in JIA. Subclinical cardiovascular involvement begins shortly after disease onset and progresses with disease duration. All cardiac structures may be affected: pericardium, myocardium, endocardium, coronary vessels, heart valves, and the conduction system. Premature atherosclerosis is aggravated by systemic inflammatory molecules and leads to ischemic coronary artery disease. This is seen more often due to the increased survival of the disease. The impairment of systolic and diastolic function has been shown. Regular follow-up with a (pediatric) cardiologist should be done in all patients with JIA, even in adulthood [13].

Patients undergoing arthroplasty should be evaluated for cardiac disease using the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. According to the ACC/AHA risk stratification algorithm, hip arthroplasty is an intermediate-risk procedure, with a 1% to 5% risk of serious cardiac events such as cardiac death or non-fatal myocardial infarction [14]. Due to the similarity of the underlying pathophysiological mechanism of the disease, this can be applied to older patients with Juvenile Idiopathic Arthritis.

## 2.3. Systemic Juvenile Idiopathic Arthritis

Even though 30-40% of these patients have a monophasic disease course, other studies have shown that this subtype carries a high risk for morbidity and mortality. Laboratory disarrangements such as anemia (microcytic, hypochromic), neutrophilic leukocytosis, thrombocytosis; elevated ESR, high ferritin, low albumin, elevated liver enzymes (mild), and elevated D-dimers occur.

Macrophage activation syndrome (MAS) is a serious complication in systemic Juvenile Idiopathic Arthritis. Diagnosis is essential because MAS can quickly progress to multi-organ system involvement and failure [15]. MAS is an overwhelming inflammatory process associated with an overproduction of pro-inflammatory cytokines. Classic laboratory findings include elevated serum transaminases, hypertriglyceridemia, consumptive coagulopathy, hyperferritinemia, and possible pancytopenia. Substantial elevations of platelet, white blood cell, and neutrophils in the setting of active systemic inflammation should raise the suspicion of MAS, although it can occur with normal blood counts.

### 3. THERAPY

Therapeutic strategies aim to control symptoms and slow progression of the disease. The use of vitamin D and calcium, physical therapy and early use of disease-modifying anti-rheumatic drugs (DMARDs), along with NSAIDs and corticosteroids, are a common approach in these patients. DMARDs include drugs such as methotrexate, leflunomide, sulphasalazine, hydroxychloroquine, tumor necrosis factor inhibitors, abatacept, and others [16].

These medications can cause metabolic, toxic, infectious and neoplastic side effects (Table 1). The ones most relevant for the anesthesiologist are usually metabolic effects (*e.g.*, decreased bone density, weight gain, *etc.*) and toxic side effects causing organ and tissue injury (*e.g.*, kidney, liver, *etc.*) [17]. Hence, laboratory monitoring is warranted for assessing pharmacological sequelae of therapy.

**Table 1. Relevant side effects from therapy [18].**

Medication	Clinical Side Effects and/or Abnormal Laboratory Values
Methotrexate	Stomatitis, pneumonitis, pulmonary fibrosis Elevated liver enzymes.
Sulfasalazine	Abnormal liver function tests.
Leflunomide	Abnormal liver function tests.
All biologic DMARDs	Increased infection risk, both common (such as pneumonia, cellulitis, and urinary tract infection) and uncommon (such as tuberculosis and fungal infection).
Glucocorticoids	Increased infection risk, hyperglycemia, hypertension, osteoporosis, weight gain, mood instability, psychosis, sleep disturbances [16].

### 4. PREOPERATIVE EVALUATION

Patients with Juvenile Idiopathic Arthritis require individual preoperative evaluation due to their various musculoskeletal and non-musculoskeletal manifestations of the disease [4]. Clinicians must be especially aware of potential airway compromise. This can be identified and evaluated by medical history and physical exam.

#### 4.1. Compromised Airway

Mandibular opening, visibility of oropharyngeal landmarks upon opening and size of the mandibular space should be carefully evaluated. Children with JIA undergoing surgical procedures are at higher risk of developing a compromised airway and respiratory failure, which is notable considering pediatric airway anatomy and physiology poses a risk factor, even in healthy children. In general, children have a higher basal metabolic rate with an oxygen consumption of about twice that of adults. Pediatric patients are more likely to develop rapid desaturation or hypoxemia during apnea, loss of airway patency or inadequate ventilation [8]. Respiratory complications represent the greatest cause of intraoperative anesthetic morbidity in children. Murat *et al.* described this in a large study cohort of 2465 pediatric anesthetics performed over a 30-month period in which 53% of all intraoperative events were respiratory complications [19].

Patients with Juvenile Idiopathic Arthritis also have a

higher risk of developing complications during outpatient parenteral and enteral moderate sedation compared with their healthy peers. The risks remain the same with the administration of general anesthesia. In-office moderate sedation may be contraindicated in these patients, and only small, short procedures should be completed by individuals who are adequately trained [8]. For these reasons, advanced airway equipment must be available at all times.

When general anesthesia is indicated in patients with Juvenile Idiopathic Arthritis with a high risk of respiratory complications, pulmonary function testing preoperatively and utilization of direct fiberoptic visualization of the airway may be needed for optimal airway management of general endotracheal anesthesia [5].

#### 4.2. Medications

Medications used to manage the patient's inflammatory disease should be carefully reviewed as they have specific implications for anesthetic management and can interfere with wound healing and precipitate perioperative infections. On the contrary, withholding these medications can cause a flare of the disease and compromise rehabilitation.

Most studies involving medication guidelines in patients with Juvenile Idiopathic Arthritis were conducted with patients undergoing Total Hip (THA) or Total Knee Arthroplasty (TKA). Ravi *et al.* found that TKA recipients with RA were at increased risk for infection compared to patients with OA (1.2% versus 0.8%,  $p = 0.02$ ). Even after controlling for potential confounders, a diagnosis of RA remained as a significantly increased risk of infection (adjusted HR 1.47 [95% CI 1.05-2.05],  $p = 0.03$ ) [20].

Administering or withholding one's anti-rheumatic medications during the perioperative period varies widely among institutions. To reduce the risk of intraoperative bleeding and possible interference with bone growth, bone graft incorporation and wound healing, NSAIDs and DMARDs should be discontinued for at least ten days before surgery and up to six weeks afterward if possible [21].

Goodman *et al.* published a Practice Guideline in 2017 to address perioperative medication management in this patient population. They constructed this practice guideline incorporating input from a patient panel and addressed the importance of patient preference when evidence quality was not high. The topics addressed by this guideline include: 1) Should anti-rheumatic medications be withheld prior to elective Total Hip Arthroplasty/Total Knee Arthroplasty? 2) If they are withheld, when should they be stopped? 3) If withheld, when should they be restarted after surgery? 4) In patients receiving glucocorticoids, what dose should be administered at the time of surgery [22]. They used the GRADE methodology to synthesize the best available evidence and a patient panel to incorporate their view on this issue.

The patient panel consisted of 11 patients with Rheumatoid Arthritis or Juvenile Idiopathic Arthritis, all of whom had at least 1 surgical joint replacement. The panel rated the risk of infection by a continued medication more important than a possible flare when the medication is stopped, even though

flares are more common than infections. They explained this preference by stating they “always expect to flare” as they can better deal with this known risk, whereas an infection might prolong recovery and might introduce other health issues [23]. According to these guidelines, patients with JIA receiving non-biologic DMARDs should continue the current dose of methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine when undergoing elective THA or TKA. Current biologic agents should be withheld before surgery in patients undergoing elective THA or TKA and the surgery should be scheduled at the end of the dosing cycle for that specific medication. Tofacitinib should be held for at least seven days prior to surgery in patients with JIA undergoing THA or TKA. These medications can be restarted once there is evidence of wound healing (typically ~14 days), surgical sutures are removed and there is no significant swelling, erythema, drainage, and no clinical evidence of non-surgical site infections [22].

Patients on long-term corticosteroids are at risk for adrenal insufficiency. When undergoing surgical procedures, *e.g.*, arthroplasty, a stress dose of 100 mg hydrocortisone intravenously should be administered. Major surgical procedures, *e.g.*, simultaneous bilateral arthroplasty, require four additional bolus doses of steroids every eight hours after the first dose and can then be gradually tapered [24].

## 5. ANESTHESIA MANAGEMENT

The anesthetic plan depends on the type of procedure and the condition of the patient. We will discuss one procedure with the respective anesthetic plan as well as the use of specific agents in detail below.

### 5.1. Local Anesthetics and Intra-articular Injection

Intra-articular corticosteroid injections are a cornerstone for the management of Juvenile Idiopathic Arthritis. The procedure itself is usually short but can be associated with pain and anxiety. Another difficulty is young patient age, especially when it comes to holding still for the procedure and cooperation. For first time recipients, reducing anxiety and pain is paramount to laying a good foundation for future procedures. The anesthetic plan for intra-articular injections can consist of local anesthetics, conscious sedation or general anesthesia.

Several local anesthetic formulas are utilized, such as eutectic lidocaine/prilocaine (EMLA) cream, subcutaneous lidocaine, and ethyl chloride spray [25]. EMLA is usually applied to the skin under an occlusive dressing prior to the procedure. After 60 minutes, EMLA has been shown to have an analgesic depth of 3 mm underneath the skin. The synovial membrane that will be penetrated by the needle during intra-articular joint injection is usually deeper than 5 mm. This is thought to explain the ineffectiveness of analgesia during intra-articular joint injection [25]. For this reason, a subcutaneous injection of lidocaine 2% solution is commonly used for procedures including joint injection [26].

### 5.2. Conscious Sedation

Non-invasive monitoring and short-acting sedative drugs make conscious sedation a safe option outside the operating

room. Often used pharmacologic agents are nitrous oxide sedation, benzodiazepines, ketamine, propofol, and fentanyl.

#### 5.2.1. Nitrous Oxide

Nitrous oxide is a volatile gas with analgesic, anxiolytic and sedative properties. It can be administered up to 70% concentration with oxygen by mask for pediatric procedural sedation and is used particularly for short (<15 minutes) procedures [27]. Studies confirmed safe and effective analgesia in children receiving intra-articular joint injection while receiving an inhaled N<sub>2</sub>O mixture [28, 29]. Nitrous oxide is often readily available and allows for avoidance of risks associated with intravenous sedation and general anesthesia, thus shortening the hospital stay. However, the mask that is necessary for conscious sedation with nitrous oxide may provoke anxiety in children. Nitrous oxide sedation can be combined with distraction techniques to shift the patient's focus away from the procedure and pain, promote a comfortable atmosphere, and make the procedure easier to perform. Research has shown that this can improve pain levels and promote comfort. It should be noted that nitrous oxide can induce nausea, and prophylaxis should be considered [25].

#### 5.2.2. Benzodiazepines

Benzodiazepines have anxiolytic, amnestic, sedative, hypnotic, muscle relaxant, and anticonvulsant properties. They can be administered *via* the oral, rectal, nasal, intramuscular and intravenous route. The most commonly used benzodiazepine for procedural sedation is midazolam. With intravenous administration of midazolam, a rapid time to peak effect (2-3 min) with a relatively short duration of action (45-60 min) can be achieved. Paradoxical reactions, including inconsolable crying, dysphoria, agitation, disorientation, and restlessness, have been described with the use of midazolam and the reported incidence ranges between 1-15% in children [30]. Benzodiazepines have no analgesic property, so for painful procedures, it is often administered together with an opioid. Benzodiazepines cause dose-dependent respiratory depression. Caution must be exercised when using benzodiazepines and opioids together since the risks of hypoxia and apnea are significantly greater than when either is used alone [31].

#### 5.2.3. Ketamine

Ketamine hydrochloride is administered by oral, intravenous and intramuscular routes and is capable of providing both sedation and analgesia without significantly inhibiting respiratory drive. With intravenous administration, peak plasma concentration is achieved within 1 minute. This allows for an immediate clinical effect. Intravenous administration allows deep levels of sedation to be achieved with good tolerance for painful procedures. By sympathetic stimulation, ketamine can lead to an increase in blood pressure and heart rate, as well as intracranial pressure. Other side effects include increased salivation and vomiting. The occurrence of laryngospasm and apnea is rare. Safety of ketamine sedation among children has been widely reported [25].

#### 5.2.4. Propofol

Propofol is a hypnotic and sedative agent, with no analgesic effects. It is ultra-short-acting, with the fastest onset of action and short recovery time compared to other commonly used drugs. Within 30 seconds of intravenous administration, the clinical effect is usually achieved. Adverse effects occur in 2-5% of children undergoing propofol sedation. The narrow therapeutic window proposes the main disadvantage of propofol use in procedural sedation. Respiratory events, such as upper airway obstruction, respiratory depression, and apnea, can require intervention by a trained provider, including the management of a patient under general anesthesia when the loss of reflexes occurs. Hypotension necessitating further management may occur [25]. With vigilant monitoring by highly skilled practitioners, propofol is well suited for short, painful procedures [32].

#### 5.2.5. Fentanyl

Fentanyl is a potent opioid with no intrinsic anxiolytic or amnestic properties. A single intravenous dose has a rapid onset (<30 s) with a peak at 2-3 min and a brief clinical duration (20-40 min). Its effects can be reversed with opioid antagonists (i.e., naloxone) [30]. It is often combined with sedative-hypotonic agents to add analgesic properties for painful procedures. Hypoxemia, respiratory depression, and apnea may occur when fentanyl is combined with other sedatives (e.g., propofol, midazolam). Chest wall and glottic rigidity are rare, but are life-threatening adverse effects of fentanyl. Accordingly, fentanyl should be given only by an anesthesiologist or by a non-anesthesiologist physician who has undergone a specialized sedation course and when adequate facilities for pediatric resuscitation are available [25].

#### 5.3. General Anesthesia

Young children, or those requiring multiple joint injections, will require general anesthesia. Most institutions perform intra-articular joint injections under general anesthesia in children under the age of three years. As gradual joint destruction often requires joint replacement, many patients with Juvenile Idiopathic Arthritis will likely undergo surgical interventions also requiring general anesthesia. Drugs used for general anesthesia are the same as for conscious sedation simply in larger doses. The greater depth of anesthesia requires a secure airway and standard anesthetic monitoring in an operating theatre.

### 6. POSTOPERATIVE CARE

Multiple sequelae of JIA can predispose patients to postoperative respiratory failure. A restrictive lung disorder predisposes patients to hypoventilation, atelectasis, pulmonary infection, and hypoxemia, especially when the diaphragm is fixed due to pain, obesity or bandages. Immunosuppressive agents can predispose to pulmonary infections in susceptible patients.

Fixation of the spine can leave the patient bedridden, making thoracic physiotherapy more difficult thus, passive exercises can reduce the worsening or development of contractures and should be initiated as soon as possible.

Whenever appropriate, protective corticosteroids should be continued. In high-risk patients, prophylactic methods for peptic ulcers or ulceration should be used. Renal function should be carefully monitored in the postoperative period in situations of prior renal impairment superimposed on drug nephrotoxicity and hypovolemia, reducing renal blood flow [33].

#### 6.1. Acute Pain Management

In patients with JIA, a multimodal pain approach is suggested [34]. Pain may be linked to the underlying disease. Thus, the treatment of arthritis is important. In cases of acute onset of JIA, bridging therapy with glucocorticoids may reduce the pain. The route of administration of glucocorticoids can be either intravenous or intra-articular [35]. As discussed above, intra-articular corticosteroid injections pain can be best controlled by choosing the most appropriate level of sedation and respective medications for the patient. In addition, NSAIDs and acetaminophen can be administered to children with mild pain. For more severe pain, opioids can be used. Physical and psychological therapy should be incorporated into a multimodal approach [34]. We assume that pain perception and processing in patients with JIA are altered and thus might not be appropriately addressed by our current pain regimen. However, further research is warranted to learn more about how to manage pain in this patient population (Table 2).

**Table 2. Key points for the management of patients with Juvenile Idiopathic Arthritis.**

Anesthesia Management	Anesthesia Strategy to Overcome Challenges
Preoperative management	Assess for anatomical abnormalities and systemic disease Identify the type of procedure being performed Evaluate the need for modification of current drug regimen
Intraoperative management	Local anesthetics: - Lidocaine/Prilocaine (EMLA) cream - Subcutaneous Lidocaine - Ethyl chloride spray Conscious sedation: - Nitrous oxide - Benzodiazepines - Ketamine - Propofol - Fentanyl General anesthesia: - same drugs as in conscious sedation but a higher dose - warrants a secure airway and anesthesia monitoring
Postoperative Management	Consider underlying disease/medications to prevent complications Use a multi-modal approach for pain management

### CONCLUSION

This review describes current anesthesia practices in patients with Juvenile Idiopathic Arthritis, a chronic disease with varying degrees of joint and systemic involvement. This patient population has several disease-related sequelae that often require surgical interventions, and research investigating current practices is sparse. However, this review serves to

summarize recent studies investigating different aspects of current practices and difficulties related to anesthetic care in these patients.

Patients with Juvenile Idiopathic Arthritis require thorough preoperative evaluation due to the musculoskeletal and non-musculoskeletal manifestation of their disease [4]. Important perioperative considerations include the risk of airway compromise and endotracheal placement, the presence of coronary artery disease and the potential for postoperative respiratory failure. Currently, different practices exist in regard to perioperative medication management, especially the DMARDs and biological agents. Goodman *et al.* published a Guideline for the Perioperative Management of Antirheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty in 2017 that can be used as a reference for these patients and adapted for patients with Juvenile Idiopathic Arthritis undergoing other surgical procedures [22].

#### CONSENT FOR PUBLICATION

All patients participated on a voluntary basis and gave their informed consent.

#### AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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