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CLINICAL VIGNETTE

Regional Anesthesia in a Patient with Familial Mediterranean Fever

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Introduction

Familial Mediterranean Fever (FMF) is a rare hereditary condition characterized by recurrent episodes of painful inflammation. These pain episodes occur most commonly in the abdomen, but can also involve the chest, joints, and rarely the heart, as well as membranes surrounding the brain, spinal cord, and testicles.[1-4] Abdominal crisis occurs in 95% of cases, although patients with uncomplicated FMF are usually asymptomatic.[4,5] Attacks can be accompanied by fever, rash and headaches[1-3,6] and may develop within 1-2 hours following a triggered event such as emotional stress.[4,7] Episodes vary in intensity and usually last 12 to 72 hours.[2,4,5] The onset of attacks usually occurs prior to age 20 and decrease in frequency with aging.[1] FMF predominantly affects people of Armenian, Arab, Turkish, or Jewish descent from the Mediterranean region with a reported prevalence from 1 in 200 to 1,000 in these populations and less common in other populations.[1-3,5,6]

Patients have developed serositis and fever triggered by the physical and emotional stress from surgery and anesthesia, including spinal anesthesia.[4,7] Little is known about the anesthetic considerations to prevent and abort intraoperative pain episodes in patients with FMF. We present a 53-year-old female with FMF who underwent regional anesthesia and monitored anesthesia care (MAC) for bunionectomy.

Case Presentation

A 53-year-old female, American Society of Anesthesiologists classification III, underwent bunionectomy for recurrent left foot bunion. She has FMF and is followed by rheumatology with symptoms of fever and serositis triggered by stress and anxiety. Episodes were controlled for the past six months on outpatient oral colchicine therapy 0.6 mg twice a day. In addition to FMF, past medical history includes hyperlipidemia, bilateral hand arthritis, bilateral partial rotator cuff tears and history of chest pain with negative workup. Her other medications included dilofenac 1% topical gel, atorvastatin, folic acid, and methotrexate. The patient had no known drug allergies and negative family medical history. Prior surgeries included appendectomy, hysterectomy, and prior foot procedures. She reported no previous problems with anesthesia, including an ankle block for her previous left foot metatarsal osteotomy. Review of systems was negative on presentation. Preoperative vital signs were within normal limits: temperature 36.2°C, heart rate 64 beats per minute, respiratory rate 20 breaths per minute, blood pressure 114/56 mmHg and a BMI of 26.1 kg/m2.

Preoperative airway exam demonstrated adequate mouth opening, a Mallampati class II airway, full cervical neck range of motion, midline trachea, and adequate thyromental distance. Physical exam, including cardiac and respiratory exam, was unremarkable. Her ECG was notable for baseline flat t-waves in leads V3 and V4, which the patient had on prior ECG. Echo was unremarkable with trace mitral regurgitation and slightly thickened mitral valve leaflets. Laboratory studies were unremarkable.

Patient was instructed to continue her prophylactic colchicine 0.6 mg tablet twice a day peri-operatively. On the day of surgery, the patient took her home colchicine medication, as instructed. In the operating room, the patient was given oral midazolam for anxiolysis and intravenous fentanyl for pain control prior to the performance of a left ankle peripheral nerve block. The American Society of Anesthesiology standard monitors (pulse oximetry, noninvasive blood pressure, EKG, and capnography) were placed. The patient was positioned supine, head neutral, and had all pressure points padded. All five peripheral nerves of the left ankle were identified by anatomic landmarks and local anesthetic solution of ropivacaine 0.5% and lidocaine 1% mixture was used for the left ankle peripheral nerve block. Padded ankle tourniquet was used to maximize patient comfort. Intravenous propofol was titrated to the patient's level of sedation during the surgery. The patient maintained spontaneous respirations throughout the procedure with 6 L/min of supplemental oxygen via face mask. The patient's vital signs remained stable throughout the 3-hour uneventful procedure. At the conclusion of surgery, the patient was transported to the post-anesthesia care unit (PACU) with continued oxygen supplementation at 8 L/min via face mask. She continued to do well in the PACU and was later discharged home the same day.

Discussion

Given the possibility and severity of perioperative pain crises associated with patients with FMF, anesthetic goals should focus on stress and anxiety reduction and the prevention of acute attacks. Careful consideration of each patient's needs is important in providing high quality and safe anesthesia care.

Preoperative Management

Since the 1970's, colchicine has been identified as the treatment of choice for FMF.[1] It is a lifelong treatment, but is only

effective as prophylaxis and ineffective for acute attacks. The drug can prevent attacks by controlling inflammation and halting the development of secondary amyloidosis, the most serious complication of the disorder, which can eventually lead to kidney failure.[1,2,5] Specifically, colchicine inhibits neutrophil chemotaxis, a step necessary for the inflammatory episodes in FMF.[1]

Because of the medication's efficacy in preventing acute attacks, it is ideal to optimize the dosing of the drug prior to proceeding with surgery. Dosing depends on a patient's age and their frequency and severity of symptoms. Children under the age of five are given a dose between 0.03-0.07 mg/kg/day.[1] Children beyond the age of ten and adults typically require a colchicine dose of 1 mg.[1,8] Complicated FMF patients with frequent crises or identified amyloidosis should receive a higher daily dose of 2-2.5 mg, with maximum dose up to 3 mg in adults as tolerated given normal liver and kidney functions.[1,8] We recommend patients to be compliant with their home colchicine prior to performing surgery to prevent intraoperative complications.

Serial monitoring of acute-phase reactants in the blood, such as fibrinogen, erythrocyte sedimentation rate, serum amyloid A (SAA) protein, and C-reactive protein (CRP), should be monitored at least every 3 months and can help to assess patient compliance and response to their treatment.[1,6,8,9] The progression to amyloidosis can be prevented by maintaining normal concentrations of the precursor protein SAA, specifically below 10 mg/L. This is the preferred acute-phase reactant to monitor.[8] CRP is a nonspecific alternative for monitoring if SAA protein assays are unavailable.[8]

Non-responding or resistant FMF patients with uncontrolled attacks despite maximum tolerated dose of colchicine for at least 6 months should consider alternative treatments. Anti-interleukin-1 (IL-1) agents should be considered if inflammation cannot be adequately controlled with colchicine therapy and are recognized as promising second-line therapies with reported significant reduction in the frequency of attacks in small randomized controlled trials.[8-11] IL-1 inhibitors such as canakinumab (human immunoglobulin G against IL-1 beta) and anakinra (a recombinant Il-1 antagonist) are currently being studied for their efficacy against FMF attacks.[1,8,9,11] Given that there is no current evidence that these alternative biological therapies can prevent the development of amyloidosis in patients with FMF, colchicine should be co-administered to combat the risk of amyloidosis despite the persistence of pain episodes.[8] There are also reported refractory FMF cases successfully treated with spinal cord stimulation with reduced frequency of pain crises.[3]

Intraoperative Management

Stressful factors, including the administration of anesthesia and surgery, can lead to FMF crises despite prophylactic use of colchicine.

One report of an intraoperative FMF episode developed following administration of spinal anesthesia for a patient receiving pilonidal sinus surgery.[4,7] The 20-year-old male patient reported severe intraoperative abdominal pain similar to the pain of an FMF attack.[4,7] He had been taking colchicine 2 mg/day for treatment of FMF for 3 years without exacerbation of attacks within the last year prior to surgery.[4,7] The pain eventually resolved within 8 minutes after administration of intravenous fentanyl and diclofenac and the surgery proceeded.[4,7]

There are potential intraoperative problems in patients with FMF. Prior to the start of surgery, a patient's level of anxiety and stress should be assessed. Oral midazolam can be given for anxiolysis as needed. Patient's oxygen saturation should be monitored as it can drop in those experiencing attacks and supplemental oxygen may be provided as needed.[9] Colchicine is not used to abort acute episodes and may even lead to diarrhea and worsening gastrointestinal complaints during a pain crisis.[1] There are no effective therapies for acute crisis and only supportive measures can be provided. If an acute crisis occurs, ensure the patient is in the supine position and deepen the level of anesthesia in an attempt to alleviate the crisis. Given reports of intraoperative crisis successfully treated with intravenous fentanyl, it can be given for prophylactic pain control. Adequate levels of sedation should be considered prior to administration of a spinal or regional block.[4,7] Non-steroidal anti-inflammatory drugs such as diclofenac, indomethacin, and naproxen are also used for supportive pain therapy.[1,8,12] Several small studies proposed alternative therapies, including the use of IL-1 inhibitors as an effective treatment for acute attacks, but other studies report no clear evidence of efficacy.[1,8,12]

One report recommended the avoidance of all types of anesthesia, including regional anesthesia, in patients with auto-inflammatory syndromes given that they are more likely to experience worsening inflammation and/or intracranial pressure of the meninges.[9,13] However, there is no compelling evidence for the absolute contraindication of neuraxial blocks in FMF patients especially given reported cases of uncomplicated regional anesthesia.[14]

Conclusion

Although FMF is a relatively rare hereditary condition in the general population, patients with such disorder may have serious complications of painful inflammation and fever. These pain attacks can be triggered by surgery or anesthesia administration, including spinal anesthesia. Our 53-year-old female patient with FMF safely underwent regional anesthesia, MAC anesthesia, and podiatric surgery. However, given the potential for serious perioperative pain episodes in these patients, it is important to carefully consider anesthetic goals focusing on stress and anxiety reduction and prevention of acute attacks as well as becoming familiar with emergency management.

REFERENCES

1. **Bhatt H, Cascella M**. Familial Mediterranean Fever. 2021 Jan 16. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 32809589.
2. Familial Mediterranean fever: *MedlinePlus Genetics*. (2020, August 18). Retrieved May 2021, from https://medlineplus.gov/genetics/condition/familial-mediterranean-fever/#inheritance
3. **Kapur S, Mutagi H, Raphael J**. Spinal cord stimulation for relief of abdominal pain in two patients with familial Mediterranean fever. *Br J Anaesth*. 2006 Dec;97(6):866-8. doi: 10.1093/bja/ael279. Epub 2006 Oct 24. PMID: 17062615.
4. **Simon A, van der Meer JW, Drenth JP**. Familial Mediterranean fever--a not so unusual cause of abdominal pain. *Best Pract Res Clin Gastroenterol*. 2005 Apr;19(2):199-213. doi: 10.1016/j.bpg.2004.11.009. PMID: 15833688.
5. **Radisic M, Santamarina J, Froment R**. Sustained, progressive, nonresolving abdominal pain: a previously undescribed clinical presentation of familial Mediterranean fever. *Clin Rheumatol.* 2006 Nov;25(6):914-6. doi: 10.1007/s10067-005-0093-1. Epub 2005 Dec 3. PMID: 16328089.
6. **Hageman IMG, Visser H, Veenstra J, Baas F, Siegert CEH.** Familial Mediterranean Fever (FMF): a single centre retrospective study in Amsterdam. *Neth J Med*. 2019 Jun;77(5):177-182. PMID: 31264586.
7. **Sert H, Muslu B, Usta B, Gözdemir M**. Familial Mediterranean fever abdominal pain during spinal anaesthesia. *Br J Anaesth*. 2009 Jul;103(1):139. doi: 10.1093/bja/aep158. PMID: 19546210.
8. **Özen S, Batu ED, Demir S**. Familial Mediterranean Fever: Recent Developments in Pathogenesis and New Recommendations for Management. *Front Immunol*. 2017 Mar 23;8:253. doi: 10.3389/fimmu.2017.00253. PMID: 28386255; PMCID: PMC5362626.
9. **Lauro CF, Goldbach-Mansky R, Schmidt M, Quezado ZM.** The anesthetic management of children with neonatal-onset multi-system inflammatory disease. *Anesth Analg*. 2007 Aug;105(2):351-7. doi: 10.1213/01.ane.0000270764.99119.1b. PMID: 17646489; PMCID: PMC3380421.
10. **Hashkes PJ, Spalding SJ, Giannini EH, Huang B, Johnson A, Park G, Barron KS, Weisman MH, Pashinian N, Reiff AO, Samuels J, Wright DA, Kastner DL, Lovell DJ.** Rilonacept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. *Ann Intern Med*. 2012 Oct 16;157(8):533-41. doi: 10.7326/0003-4819-157-8-201210160-00003. Erratum in: *Ann Intern Med.* 2014 Feb 18;160(4):291-2. PMID: 23070486.
11. **Roldan R, Ruiz AM, Miranda MD, Collantes E**. Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. *Joint Bone Spine*. 2008 Jul;75(4):504-5. doi: 10.1016/j.jbspin.2008.04.001. Epub 2008 Jun 9. PMID: 18541452.
12. **Sarı İ, Birlik M, Kasifoğlu T**. Familial Mediterranean fever: An updated review. *Eur J Rheumatol*. 2014 Mar;1(1):21-33. doi: 10.5152/eurjrheum.2014.006. Epub 2014 Mar 1. PMID: 27708867; PMCID: PMC5042258.
13. **Bissonnette B, Luginbuehl I, Marciniak B, Dalens B**, eds. Familial Mediterranean Fever. *AccessAnesthesiology*. Retrieved May 2021, from https://accessanesthesiology.mhmedical.com/content.aspx?bookid=852§ionid=49517556
14. **Weir PS, McLoughlin CC**. Anaesthesia for caesarean section in a patient with systemic amyloidosis secondary to familial Mediterranean fever. *Int J Obstet Anesth*. 1998 Oct;7(4):271-4. doi: 10.1016/s0959-289x(98)80052-6. PMID: 15321193.