Pediatric Anesthesia CME Program

Module 1

Module 1 of CSA's Pediatric Anesthesia CME Program appears in this issue of the *Bulletin*; this is the first module of this program which will consist of four modules. One module will appear in each issue of the *CSA Bulletin* consecutively. To receive CME credit, submit your registration page, answers to the questions, and evaluation to the CSA office. Your CME certificate will be mailed to you. Alternatively, the full text of each module will be accessible through the CSA Website, **www.csahq.org**, in the Online CME Program section. Instructions to complete Module 1 online are given in the Information pages. After completing the assessment, print your CME certificate. Members will need their usernames and passwords to do the modules online.

The following Important Information about Critical Care Module 1 must be read and acknowledged before proceeding to the rest of the module. Check the acknowledgement box on the registration page.

Faculty/Disclosures

All faculty participating in continuing medical education activities sponsored by the CSA are required to disclose any real or apparent conflict(s) of interest related to the content of their presentation(s) or any of the industry sponsors of the activity. In addition, speakers must disclose when a product is not labeled for the use under discussion or when a product is still investigational.

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Dr. Kim has no relevant financial relationships with any commercial interests.

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Registration/Instructions

Method of Participation: The physician will read and study the materials and complete a quiz and an evaluation of the module. Some modules may have slides available online. To register for and complete this module: Complete the registration page, complete the test questions and the evaluation that can be found after the article, and submit your quiz to the CSA office by mail or fax (650-345-3269). Your CME certificate will be mailed to you.

Estimated Time to Complete the Module: One hour

Please check the box on the registration page to acknowledge that you have read everything in these introductory pages.

Availability

Module 1: Sickle Cell Disease

Release Date: June 30, 2010
Expiration Date: June 30, 2013

CME Sponsor/Accreditation

The California Society of Anesthesiologists is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The California Society of Anesthesiologists Educational Programs Division designates this critical care program for a maximum of 4 *AMA PRA Category 1 Credit(s)*™. The program consists of four modules with one credit per module. Physicians should claim credits commensurate with the extent of their participation in the activity.

Fees, Target Audience, Evaluation

The modules are free to CSA members. Nonmembers pay $30 for each module. Each module is worth *one AMA PRA Category 1 Credit*™. This program is intended for all licensed physicians, including residents. An evaluation of each module of this series is offered after the test questions.

Privacy Policy

CSA has a privacy policy that is a general policy for information obtained regarding all online interactive pages, including online CME activities. To review this policy, please go to www.csahq.org/privacy.vp.html.

Objectives

Upon completion of this activity, participants will be able to:

- Discuss sickle cell disease and its medical management
- Cite relevant studies regarding sickle cell patients and anesthesia
- Develop an anesthetic plan for the perioperative management of a sickle cell patient
- Recognize limitations in anesthetic management

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Sickle Cell Disease

By Tae W. Kim, M.D., FAAP
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Prior to his current position, Dr. Kim was in practice for 14 years, the last 11 years of which were at Texas Children's Hospital, reaching the rank of Associate Professor at Baylor College of Medicine. His academic interests have been divided between the study of sickle cell disease and anesthesia and malignant hyperthermia. He has presented an ASA Refresher Course on sickle cell disease. He serves as a Hotline Consultant for the Malignant Hyperthermia Association of the U.S. Dr. Kim is a member of the ASA Committees on Pediatric Anesthesia and Standards and Practice Parameters and a member of the Society for Pediatric Anesthesia Sickle Cell Interest Group.

Introduction

Sickle cell disease is a medical condition that is commonly recognized, but its anesthetic implications are not generally familiar to most anesthesiologists. The population at risk extends beyond African Americans and includes people from the Mediterranean countries, Africa, the Middle East and the Asian Subcontinent.[1] In addition, the mobile nature of today's world and the increasing number of cross-cultural marriages enables this autosomal recessive disease to easily spread to other parts of the world and increases the probability of caring for someone afflicted with this disease among descendants of families from these regions.[1] In the United States, one in 500 African Americans has sickle cell disease, while one in 12 is a carrier for the disease and one in 36,000 Hispanic Americans has the disease according to the Centers for Disease Control.*

The basic biochemical defect lies in the substitution of thymine for adenine on chromosome 11, resulting in a substitution of valine for glutamic acid on the

* http://www.cdc.gov/NCBDDD/sicklecell/data.html. Last accessed 6/12/2010.

sixth position of the β-globin gene.[1] This alteration leads to an unstable β-globin chain. Hemoglobin is comprised of two α-globin chains and two β-globin chains. Under stressful conditions, the hemoglobin chain may polymerize and form tactoids leading to distortion of the red blood cell into a sickle shape. The pathophysiology of sickle cell disease centers around the abnormal red blood cell or sickle cell, resulting from a gene mutation, and the vasculopathy associated with the constant sickling and hemolysis. The term sickle cell disease encompasses many of the genotypes of the disease, such as SS, SC, SE, Sβ°thalassemia and Sβ+thalassemia.[2] However, sickle cell disease classically is defined as the homozygous state of having two sickle cell genes or SS. This designation signifies SS hemoglobin concentration ranging from more than 80 percent up to 95 percent.[3]

The conformational changes induced by exposure to low oxygen and pH states as the cell traverses the circulatory system result in increased fragility of the cell membrane. The sickle cell has a finite capacity to undergo reversible sickling, until the cell membrane loses its elasticity. The cell may rupture releasing iron, hemoglobin and arginase. Iron is irritating to the vessel endothelium and may cause a local inflammatory response.[4, 5] In addition, hemoglobin and arginase are known scavengers of nitric oxide, which plays a role in maintaining normal vascular tone and patency.[4, 5] The result is increased predisposition to thrombus formation, further sickling, ischemia and pain.

Early detection of hemoglobinopathies is achieved through neonatal screening programs routinely performed in all states, as well as prenatal screening using DNA analysis of samples from chorionic villi, amniocentesis and fetal blood sampling. Screening is performed by hemoglobin electrophoresis, and more sensitive tests are conducted using isoelectric focusing and high performance liquid chromatography.[1] Identification of newborns allows for early treatment to minimize the morbidity and mortality associated with sickle cell disease. A preoperative screening program to identify at-risk patients with unknown sickle cell disease status, however, has not proven as beneficial. A study conducted by Crawford et al. preoperatively screened 1,906 children of African ancestry at the Hospital for Sick Children, Toronto, regardless of their health, family history, or the planned procedure.[6] Of those screened, only one asymptomatic child with undiagnosed sickle cell disease and a negative family history was identified. The conclusion of their study was to recommend selective screening of individual patients.

Sickle cell disease patients periodically experience what is referred to as a sickle crisis. There are four types of sickle crises: vaso-occlusive, sequestration, aplastic, and hemolytic. The severity of the disease is based on the age of onset and the frequency and duration of sickle cell crises. The most chronic

and debilitating symptom of the disease is pain, resulting from the ischemia induced by thrombus formation and vasospasm. A major complication is acute chest syndrome, which is defined by the constellation of pain, fever, respiratory distress and new chest radiographic findings, and which accounts for 25 percent of sickle cell deaths. [2, 7, 8]

Medical management of sickle cell disease is targeted at reducing the occurrence of sickle cell crises by addressing key inciting events such as infections and inflammatory conditions. Sickle cell patients represent a subset of patients considered immunocompromised by the loss of their spleen, either from a splenectomy or autoinfarction, prior to seven years of age.[9, 10] This immunocompromised state makes them vulnerable to infections from encapsulated bacterium, such as pneumococcus.[1] Preventative medical care begins with early identification and prophylaxis against infection. Children at risk for sickle cell disease begin a regimen of daily antibiotics, typically penicillin, beginning at the age of two months until five years of age. In addition, a strict schedule of vaccinations is emphasized for the life of the individual.

The treatment for sickle cell disease patients ranges from conservative measures to more radical therapy. Many sickle cell patients benefit from supplemental oxygen, intravenous fluid hydration and pain management. Antibiotic therapy is instituted when indicated based on the findings of cultures. Blood transfusions are for more specific indications, such as an aplastic crisis or hemolytic crisis. Many patients on a chronic transfusion regimen have suffered from alloimmunization (making crossmatching difficult) and hemochromatosis.[11] Patients requiring frequent blood transfusions are therefore placed on an iron chelating medication such as deferoxamine or deferasirox. Bone marrow or stem cell transplantation has been attempted in patients, who are matched to suitable donors, and gene therapy holds promise to address the sickle cell defect in the future.

Preoperative evaluation of sickle cell patients should focus on their history of sickle crisis, past treatment, current therapy and comorbidities. The most common age group to suffer painful sickle crises is between 20 to 40 years of age with the most severe forms being acute chest syndrome, cerebrovascular accidents and priapism.[10] Those individuals suffering three or more episodes a year have an increased risk of death.[10]

The history of blood transfusions is especially important in determining whether the patient is in optimal condition. The life span of normal red blood cells is 120 days. In contrast to normal red blood cells, sickle cells have a life span of approximately 15 days. The knowledge of a blood transfusion within the past month may indicate that the percentage of sickle cells may be significantly

lower, and therefore the probability of a sickle crisis reduced under the stress of surgery and anesthesia. The importance of reducing the percentage of sickle hemoglobin through a blood transfusion was validated by a study looking at sickle cell patients undergoing cholecystectomies. Haberkern et al. enrolled 364 sickle cell patients into four groups based on whether the patient was randomized, received a blood transfusion or no blood transfusion.[12] The group with the highest incidence of sickle cell events (32 percent) was the non-transfused group. An alternative approach to blood transfusions has been to stimulate the production of fetal hemoglobin. The increased production of fetal hemoglobin has shown a significant amelioration of sickle cell complications with the reduction of sickle hemoglobin to less than 85%.[13] This is the premise of hydroxyurea therapy, which stimulates the production of fetal hemoglobin with a target of 15 percent to 20 percent.[13]

The role of blood transfusions in the perioperative management of sickle cell patients is highly dependent on the indications for a blood transfusion. The traditional approach to a preoperative blood transfusion was an aggressive transfusion to reduce the proportion of sickle cells to ≤30 percent and raise the hemoglobin to 10 gm/dL. However, a study by Vichinsky et al. demonstrated a simple blood transfusion to raise the hemoglobin to 10 gm/dL was as effective as an aggressive transfusion in preventing perioperative complications. This conservative approach was found to have less transfusion related complications.[14] Also, studies comparing the complexity and location of surgery and the indications for blood transfusion found transfusions in minor operations, such as placement of ear tubes, to be unnecessary, while operations posing a greater risk—intrathoracic, neurologic, orthopedic or laparoscopic surgery—necessitated a reduced sickle hemoglobin concentration to avoid perioperative complications.[15, 16, 17, 18, 19]

Sickle cell patients must be evaluated for co-morbid conditions. Beyond the chronic anemia ranging from 6-9 gm/dL, the cardiopulmonary system is affected by repeated episodes of sickling in the microvasculature or development of hemochromatosis, and therefore, the patient may manifest decreased cardiac function, elevated pulmonary pressures and poor gas exchange.[20, 21, 22] In addition, the hepatorenal system may be affected by the development of cirrhosis—whether from hemochromatosis, blood borne infection or intravascular sickling—and renal dysfunction resulting from intramedullary sickling and papillary necrosis.[23] Central nervous system involvement may present as transient ischemic attacks or a more severe cerebrovascular accident and its consequent neurologic deficits.[24]

Laboratory studies should be based on a thorough examination of the patient and the anticipated operation. A minimalist approach for a simple, routine

operation, such as exam under anesthesia, myringotomies and tube insertion, would be to order a complete blood count. More complex procedures, such as a laparoscopic cholecystectomy, may additionally require a recent hemoglobin electrophoresis or documentation of a blood transfusion.[10] A type and cross for blood should be ordered in advance of the operation to allow for identification of compatible blood as the sickle cell patient may have developed multiple antibodies.

Preoperative NPO orders must be timed to minimize the risk of significant dehydration. The treatment protocol of the Preoperative Transfusion in Sickle Cell Disease Study Group required at least eight hours of preoperative fluid hydration.[14] Although there are no formal guidelines, many studies have referred to preoperative hydration, preoperative intravenous fluid hydration at 1.5 times the fluid maintenance rate or encouraged oral fluid intake up to two to four hours prior to surgery.[2, 10, 12, 15,18, 25] The emphasis placed on preoperative hydration is to minimize the proportional increase in sickle hemoglobin and the propensity for sickling as a result of cellular dehydration, as well as to counterbalance the effect on blood pressure from vasodilatation. The intraoperative management of sickle cell patients centers on providing a stress free anesthetic technique. In one study looking at 4,000 patients undergoing more than 1,000 surgical procedures, it was found that more complications occurred in the sickle cell patients undergoing a regional anesthetic technique compared to a general anesthetic technique.[17] The goal is to avoid hypoxemia, hypovolemia, hypothermia and hydrogen ion accumulation (4 "H"s). Oxygen consumption increases 400 percent when shivering; therefore, it is important to maintain a neutral thermal environment to minimize the body's metabolic response in order to promote thermogenesis. Warming of intravenous fluids may also help to achieve and/or maintain normothermia. Hyperosmolar solutions, such as intravenous contrast may pose a risk of cellular dehydration of sickle cells. Blood pressure cuffs are capable of producing a tourniquet effect and must be carefully applied to minimize the risk of this side effect. The reduction or interruption of blood flow may be enough to trigger localized sickling, which could initiate a cascade effect throughout the body with the release of the tourniquet. The time interval of inflation of the blood pressure cuff should be adjusted based on the needs of the operation. Positioning and padding is important to minimize the development of venous stasis and resultant ischemia. Sickle cell patients are more at risk for peripheral neuropathies secondary to ischemia associated with sickling.

The use of tourniquets in the sickle cell population has not been validated as a safe technique. The routine use of a tourniquet for placing an intravenous catheter has not been controversial. However, the use of tourniquets to aid in a peripheral nerve block or especially for use in the operative technique has

been a topic of debate. There are no prospective randomized trials to confirm the safety of this practice. There are case reports and case series of the successful use of tourniquets in sickle cell disease patients without any perioperative complications, such as acute chest syndrome or pain.[25, 26, 27, 28] Many of these patients were from the Middle East, where those affected by sickle cell disease often have a higher percentage of fetal hemoglobin into their adulthood. In addition, many were preoperatively transfused to reduce the level of sickle hemoglobin and were closely monitored.

Vigilance in the care of the sickle cell patient should be carried into the postoperative period. Postoperative pain management may be challenging, especially when caring for individuals with chronic pain. Early intervention is needed to avoid the increased oxygen demands associated with pain-related increased sympathetic activation and release of endogenous catecholamines. Pain out of proportion to the patient's operative experience may signal the onset of a vaso-occlusive crisis. This requires immediate therapy with supplemental oxygen, continued intravenous hydration and pain medication. The decision for transfusion of blood should be based on consultation with the patient's hematologist. Acute chest syndrome has an incidence of 10 percent to 15 percent in association with intra-abdominal and joint replacement surgery.[3, 4, 7, 8] This requires immediate attention, because the mortality rate is between 2 percent to 12 percent and accounts for 25 percent of deaths in sickle cell patients.[3, 7, 8]

The best practice for anesthetic management of sickle cell patients having obstetric, cardiac and neurosurgical procedures is not well defined because of a lack of prospective randomized clinical trials. The obstetric sickle cell patient represents a high risk for complications related to pregnancy, including hypertension, preterm labor, and small-for-gestational-age baby.[29] In the most recent retrospective study of 55 pregnant women, general anesthesia was identified as a risk factor for postnatal sickling complications, which include acute chest syndrome, vaso-occlusive crisis and stroke.[30] The findings of this study run counter to the previously cited study for all-comers with surgical procedures that found regional anesthesia to be associated with a higher incidence of complications.[17] In both studies, however, the authors emphasize that the key to a well managed anesthetic is to avoid the inciting events of hypothermia, hypoxemia, hypovolemia, acidosis and hypotension.

The management of cardiac and neurosurgical patients is based mainly on case reports and case series. It traditionally has been taught to reduce the level of sickle hemoglobin to ≤ 5%.[2] The timing of such hemoglobin reduction in patients undergoing cardiac surgery is anecdotally reported, based on clinical experience with some patients receiving preoperative transfusions, while others

have been allowed to go on bypass with the expectation that the pump prime will help dilute the sickle hemoglobin concentration and preferentially filter out the sickled cells. In a more recent case series, three patients aged three weeks, three months and 18 months old underwent surgery for congenital heart disease using cardiopulmonary bypass without preoperative blood transfusion and with sickle hemoglobin concentrations ranging from 10.9 percent to 38.8 percent.[31] The children did well and the post bypass hemoglobin S concentration ranged from 4 percent to 14 percent. There also have been case reports where sickle cell patients have undergone successful cardiac surgery without a blood transfusion. However, the lack of level one evidence for a safe limit of sickle hemoglobin makes it difficult to provide level A recommendations for managing the care of these critically ill patients.

The care of sickle cell patients at high risk for a catastrophic neurologic event has continued to evolve with clinical research. Early recognition of this risk resulted in the Stroke Prevention in Sickle Cell Anemia (STOP) Trial, which recommended screening programs to detect abnormal flow velocity using transcranial Doppler ultrasonography.[24] A time-averaged mean blood-flow velocity ≥ 200 cm/sec in the internal carotid or middle cerebral artery qualified the child to be enrolled in a study regimen involving blood transfusions to reduce the hemoglobin S concentration below 30 percent. A follow-up study (STOP II) to determine how long blood transfusions are required for primary stroke prevention revealed that cessation of blood transfusions after 30 months was associated with debilitating neurologic complications.[24] Another clinical trial to determine how to wean pediatric sickle cell patients off a chronic transfusion regimen is The Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) trial. The increase in fetal hemoglobin to ≥ 15 percent is thought to reduce the incidence of complications related to the homozygous disease state.[24]

The acceptable hemoglobin S concentration for neurosurgery has not been established. In one review article there was a report of a sickle cell patient undergoing neurosurgery without a blood transfusion.[4] However, based on the literature on cerebrovascular disease in sickle cell patients, a blood transfusion to reduce the hemoglobin S concentration ≤ 30 percent with a hemoglobin around 10 gm/dL appears to be commonly accepted as safe practice. The choice of anesthetic technique is less important than the avoidance of those events that precipitate a sickle cell crisis. There have been conflicting retrospective studies examining anesthesia techniques for patients undergoing surgery for moyamoya disease.[32,33,34,35] Therefore, the focus of anesthetic management should be placed on the avoidance of inciting events for sickle cell related complications.

In summary, the anesthetic management of sickle cell patients presenting for surgery requires careful planning prior to the day of surgery. Early consultation with the patient's hematologist can provide a clear understanding of the patient's sickle cell status, comorbidities, medical therapy and especially the history of blood transfusions. The avoidance of inciting factors: hypoxemia, hypovolemia, hypotension, hydrogen ion accumulation and hypothermia is key to reducing the risk of perioperative complications. Preoperative hydration, whether orally or intravenously, is important to minimize the risk of sickling. The administration of a blood transfusion should be based on the patient's medical condition, surgical procedure and anesthetic plan. Retrospective studies on anesthetic technique are inconclusive; however, the common element in the studies has been to avoid inciting factors for sickling. Perioperative complications can occur in the post anesthesia care unit and therefore require vigilance on the part of the nursing team and anesthesiologists to recognize and identify complications associated with sickle cell disease, and to aggressively treat any early signs or symptoms related to a sickle cell crisis.

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Pediatric Anesthesia Module 1 — Sickle Cell Disease

The first module in the Pediatric Anesthesia Bulletin and Online CME Program is now available in this issue. You may do the module by taking the assessment and faxing a copy to the CSA office at 650-345-3691, or you may go online and take the module in the Online CME section of the CSA Website (http://www.csahq.org).

Questions

1. Sickle cell disease (SS) affects:
    a. Only African Americans
    b. Only males from the Mediterranean region
    c. 50 percent of offspring when both parents are genotypically AS
    d. Individuals possessing a point mutation on chromosome 11

2. The sickle shape of red blood cells results from:
    a. Conformational change due to polymerization of sickle hemoglobin
    b. Substitution of glutamic acid for valine on the globin chain
    c. Release of arginase
    d. Decrease serum osmolality

3. The earliest time to test for sickle cell disease in the baby is:
    a. Immediately after delivery using umbilical cord blood
    b. After the transition from fetal hemoglobin to adult hemoglobin
    c. In utero by chorionic villus sampling
    d. After a blood transfusion

4. Individuals with sickle cell disease require a daily regimen of penicillin because:
    a. They are at risk for infection from encapsulated bacterium
    b. They are at an increased risk for bacterial endocarditis
    c. They are at increased risk for viral infections
    d. Penicillin reduces the incidence of renal dysfunction

5. The most severe sequelae from a sickle crisis is:
    a. Acute chest syndrome, osteomyelitis, cholecystitis
    b. Cerebrovascular accident, nephrocalcinosis, osteomyelitis
    c. Acute chest syndrome, cerebrovascular accident, priapism
    d. Acute chest syndrome, cerebrovascular accident, cholelithiasis

6. Acute chest syndrome:
    a. Is a major cause of death in sickle cell patients
    b. Affects only those sickle cell patients with asthma
    c. Is associated with sinus surgery
    d. Occurs after a blood transfusion

7. The STOP II trial:
    a. Demonstrated the efficacy of a conservative transfusion therapy on a routine basis
    b. Demonstrated the continued need for blood transfusion therapy to reduce the recurrence of neurologic events
    c. Demonstrated the benefits of a simple transfusion
    d. Demonstrated sickle cell patients with a transcranial Doppler flow of greater than 200 cm/sec could be safely withdrawn from receiving blood

8. Pre-operative fluid hydration:
    a. Requires pre-admission for intravenous fluid therapy overnight
    b. Allows liberal oral fluid intake until the time of surgery
    c. Increases serum osmolality
    d. Minimizes cellular dehydration and the propensity for red blood cells to sickle

9. Retrospective studies on pre-operative blood transfusions showed:
    a. A simple blood transfusion to 10 gm/dL was superior compared to an aggressive transfusion protocol with reduction of sickle hemoglobin to below 30 percent and 10 gm/dL
    b. The perioperative sickle cell complications were similar in both transfusion groups
    c. Transfused red blood cells have a short half-life of 30 days
    d. No harmful effects beyond 10 gm/dL

10. Retrospective studies have shown:
    a. No conclusive benefit of general over regional anesthesia and vice-versa
    b. Regional anesthesia was an independent risk factor for postnatal complications
    c. Patients for cardiac surgery and bypass require hemoglobin S values below 5 percent to ensure a safe anesthetic
    d. Obstetrical sickle cell mothers have the same risks as a non-sickle cell mother

11. The use of surgical tourniquets:
    a. Has been validated with prospective, randomized control trials
    b. Is limited to use in Middle Eastern people only
    c. Isolates the extremity and therefore eliminates the need for a blood transfusion
    d. Has yet to be validated as a safe anesthetic technique in sickle cell patients

Evaluation of Module 8

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

2. How relevant was the information in this program to your clinical practice?

Very Relevant	5	Above Average	4
Average	3	Below Average	2
Not Relevant	1		

3. How would you rate this program overall?

Excellent	5	Above Average	4
Average	3	Below Average	2
Poor	1		

4. Did you detect any commercial bias in this module? Yes No

Registration

Complete this form, the test, and the evaluation, and mail all three to the CSA office at 951 Mariner's Island Boulevard #270, San Mateo, CA 94404 or fax them to 650-345-3269. The CSA CME journal courses are also available on the CSA Website at www.csahq.org.

Pediatric Anesthesia CME Course, Module 1

Available June 30, 2010, to June 30, 2013

Name _____ M.D. D.O.

Address _____

City/State/Zip _____

Phone ( ) _____

E-mail _____

❑ CSA Member (No Fee)

❑ Non-CSA Physician $30

Total $_____

Please charge my: ❑ MasterCard ❑ Visa

Card # _____ Exp. Date_____

I authorize the California Society of Anesthesiologists to charge my account for the registration.

Signature: _____

OR

Mail with a check made payable to California Society of Anesthesiologists

❑ **I acknowledge that I have read the Important Information about Module 1.**