Thrombocytopenia, low molecular weight heparin, and obstetric anesthesia

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Although neuraxial anesthesia is routinely administered to the parturient, a spinal hematoma is a rare occurrence that is primarily associated with patients who have disorders of hemostasis. A parturient with a clinically active coagulation disorder, or someone with a history of easy bruising or bleeding, is considered to have an absolute contraindication to regional anesthesia. Many areas of controversy exist, especially regarding patients with thrombocytopenia and patients who receive anticoagulant medication. The concern most anesthesiologists have regarding thrombocytopenia is determining the lowest platelet count at which it is still safe to perform a neuraxial anesthetic technique. The purpose of this article is to review the role of platelets in the coagulation process, discuss the laboratory tests available to test platelet function, and provide recommendations as to the lowest platelet count that is acceptable for neuraxial anesthesia. An increasing number of patients are receiving anticoagulant medications during pregnancy, of which low molecular weight heparin (LMWH) is one. The role of LMWH during pregnancy and its implications for labor analgesia also are discussed.

Thrombocytopenia and neuraxial anesthesia

Platelet counts generally decrease by approximately 20% during a normal pregnancy. This decrease is usually not clinically significant and does not generally impact on the decision to place epidural anesthesia. Approximately 7% of all parturients present with a platelet count less than 150,000/mm-3, however, and 0.5% to 1% present with a platelet count less than 100,000/mm-3[1].

An epidural or spinal hematoma can be a catastrophic complication that can lead to permanent paralysis. In 1988, Cousins and Bromage recommended that one should not place an epidural catheter if the platelet count is less than 100,000/mm-3[2]. Recently, their recommendation has been challenged, primarily because thrombocytopenia occurs frequently during pregnancy [1] and neuraxial anesthesia is safer than general anesthesia for the parturient [3]. An absolute platelet count below which a neuraxial anesthetic is considered unsafe would lead to more frequent use of general anesthesia, which is far riskier in the parturient.

Hawkins et al [3] reviewed pregnancy-related deaths in the United States between 1985 and 1990 and found that the anesthesia-related maternal mortality rate was 32.3 deaths per million in parturients who had general anesthesia for cesarean

delivery but only 1.9 deaths per million in patients who had regional anesthesia. There is an increasing trend toward using regional anesthesia in the parturient, so an absolute conservative cut-off for a sufficient platelet count is not prudent. Failure to provide neuraxial anesthesia during labor and delivery based solely on a low platelet count commits the patient, at a minimum, to a painful labor. If a woman later requires a cesarean delivery, perhaps emergently, the anesthesiologist may be forced to administer anesthesia under less-than-optimal conditions.

Clotting can be thought of as occurring in two phases: primary and secondary hemostasis. Primary hemostasis refers to the creation of the initial platelet plug, and secondary hemostasis refers to the creation of the stable fibrin clot. Platelets play an important role in both processes. Generally, blood vessels prevent platelet adhesion by releasing a potent vasodilator, prostacyclin. After vessel wall injury, prostacyclin levels decrease, which allows platelets to adhere to the vessel wall. This adhesion leads to activation and degranulation of platelets with release of adenosine 5-diphosphate, serotonin, and thromboxane, which then leads to platelet aggregation. Further aggregation leads to formation of a platelet plug. The plug is unstable and requires fibrin deposition to make it more stable, which occurs by activation of the intrinsic and/or extrinsic coagulation system. Platelets provide the phospholipid membrane on which the coagulation cascade occurs.

Platelet abnormalities can be qualitative or quantitative and are the most common hematologic disorders during pregnancy. Most cases (99%) of thrombocytopenia during pregnancy are related to one of three causes: hypertensive disorders, such as preeclampsia, gestational thrombocytopenia, or idiopathic thrombocytopenic purpura (ITP). When evaluating the parturient with thrombocytopenia, there are two specific issues to consider. The first concern is whether the disorder is static or dynamic. If the disorder is static, as occurs during gestational thrombocytopenia or ITP, the platelet count is usually stable. If the disorder is dynamic, as occurs during preeclampsia, the platelet count may change rapidly and it is important to obtain serial platelet counts. The second issue is whether platelet function is normal or abnormal. Platelet function is typically normal in gestational thrombocytopenia and ITP and usually abnormal in preeclampsia.

The patient with thrombocytopenia is difficult to evaluate with standard laboratory tests because platelet quantity and quality must be assessed. Tests of platelet function have been criticized for being difficult to perform, lacking reproducibility, and being of questionable clinical relevance. The ideal test should be easy to perform, inexpensive, not require specialized equipment, and the results could be reproduced and correlated with outcome. Bedside tests of coagulation include the bleeding time, thromboelastography, and newer tests such as the platelet function analyzer.

The bleeding time is a simple bedside test that evaluates the quality and quantity of the platelets. A small skin nick is made with a template on the volar surface of the forearm and the time until the blood clots is calculated. A bleeding time of less than 10 minutes is considered normal. Anesthesiologists formerly used the bleeding time to assess the safety of epidural or spinal placement. If the results of the bleeding time were normal, they would proceed with neuraxial anesthesia, and if the results were abnormal, they would not. The bleeding time is no longer recommended to determine the safety of epidural catheter placement, however, because bleeding at the test site does not necessarily reflect the risk of bleeding at other sites [4,5] and there is wide observer variation [6]. O'Kelly et al [6] asked 12 observers to assess the bleeding time on five separate volunteers. The reliability of the measurements obtained was poor among the 12 observers and the authors concluded that the test was unreliable. Although no longer recommended, a survey by Beilin et al [7] found that 48% of anesthesiologists in academic practice and 76% in private practice still used the bleeding time to assist them in deciding whether to place neuraxial anesthesia in the parturient with thrombocytopenia.

The thromboelastogram measures all phases of coagulation and fibrinolysis by using less than 1 mL of a whole blood sample to measure the elasticity of clotting blood. Blood is placed in a cylindrical cup that oscillates. A pin is then suspended in the blood by a torsion wire and is then monitored for motion. The torque of the rotating cup only affects the pin after fibrin-platelet bonding has linked the cup and pin together. The strength of the developing clot affects the magnitude of the pin motion such that strong clots move the pin directly in phase with the cup and weak clots do not. The resulting profile is a measure of the time taken for the first fibrin strand to form and the kinetics, strength, and breakdown of the clot (Fig. 1). The maximum amplitude has been found to correlate best with platelet function.

Fig. 1. Thromboelastogram (TEG): R, time until the onset of clotting.; K, time until the tracing amplitude reaches 20 mm; Angle, the angle between the tangent line drawn from the curve to the split point and the tracing's horizontal line, in degrees; MA, measures the maximum amplitude, a measure of clotting strength.

Orlikowski et al [8] measured platelet counts, thromboelastogram parameters, and bleeding time in healthy pregnant women and women with preeclampsia. They found that the maximum amplitude remained normal (53 mm) until the platelet count decreased to less than 54,000/mm-3 (95% confidence limit 40–75,000/mm-3). Based on their study, they suggested that a platelet count of 75,000/mm-3 should be associated with adequate hemostasis. There is no clinical evidence, however, that a normal maximum amplitude correlates with safe epidural analgesia.

The platelet function analyzer-100 is an intriguing test because it is specific to platelet function, the primary disorder in the parturient with preeclampsia. The machine simulates in vivo hemostatic mechanism of platelet function by accelerating citrated whole blood through a small, 150-É m aperture cut in a collagen membrane. The collagen membrane is coated with one of two platelet activators: epinephrine (EPI) or adenosine 5-diphosphate (ADP). The time taken for the aperture to close is called the closure time. This machine is commonly used by hematologists as a screening tool for patients who present with unknown coagulopathies and is especially sensitive for the detection of von Willebrand's disease [9]. Initial studies in the parturient focused on defining the expected closure time [10]. These studies found that closure time may be a more sensitive marker for bleeding than the maximum amplitude, from the thromboelastogram test, for patients with preeclampsia [11] and thrombocytopenia [12].

The overall risk of epidural or spinal hematoma after neuraxial anesthesia is in the range of 1:150,000 to 220,000 [13]. Vandermeulen et al [13] reviewed the literature and found 61 cases of anesthesia-related spinal hematoma. Most cases (68%) occurred in patients with coagulopathies, and 75% of all cases had epidural rather than spinal anesthesia. Of the patients who received epidural anesthesia, 88% had an epidural catheter inserted and almost 50% of the patients developed an epidural hematoma after catheter removal.

The authors are aware of ten reports in the literature of neuraxial (spinal or epidural) hematoma occurring in parturients. In three of these cases, the diagnoses were made clinically, and the symptoms resolved spontaneously [14–16]. Details in a fourth case are not available, but the patient did require surgery to evacuate an epidural hematoma; the patient was reported as “still improving” [17].

Three of the ten parturients had anatomic abnormalities of their spines that were not appreciated before the initiation of labor analgesia. In two cases, the patients were reportedly healthy but were later found to have a spinal ependymoma, which occurs rarely [18,19]. Another patient with neurofibromatosis developed mild neurologic symptoms postpartum, and MRI revealed a small epidural hematoma; the symptoms resolved the next day without intervention [20].

In another two of the ten cases, an epidural hematoma was reported in patients who already had disorders of coagulation, all of whom recovered fully or had only minor residual deficits [21,22]. One of these two patients presented with cholestasis of pregnancy and received labor epidural analgesia; the patient later developed an epidural hematoma and at that time was found to have an elevated prothrombin time (27.7 seconds) and partial thromboplastin time (59.1 seconds) [22]. The second woman presented with preeclampsia and had a history of a lupus anticoagulant [21]. Her preoperative laboratory tests revealed a normal platelet

count of 425,000/mm-3, prothrombin time of 10.5 seconds, and bleeding time of 3 minutes. Her partial thromboplastin time was elevated at 49 seconds, which was attributed to a lupus anticoagulant, so the decision was made to proceed with epidural anesthesia for cesarean delivery. In the operating room, the patient had a grand mal seizure after catheter placement; the epidural catheter was not used, and the operation was performed under general anesthesia. The next day, the patient complained of leg weakness and an MRI showed an epidural hematoma that was subsequently evacuated.

The tenth case occurred in a woman with preeclampsia who had a platelet count of 71,000/mm-3[23]. The patient had epidural anesthesia with 13 mL of bupivacaine 0.5% for uneventful cesarean delivery but had a seizure in the recovery room 1 hour after the procedure. It was noted that her legs did not move and a CT scan revealed an epidural collection of fluid. A laminectomy was performed 6 hours after epidural catheter placement, at which time 4 mL of blood were drained from the epidural space. The patient recovered 72 hours later. Whether the 4 mL fluid collection was sufficient to cause her symptoms is unknown; it is possible that the symptoms were related to residual local anesthetic effects.

The origin of the recommendation to not place an epidural catheter if the platelet count is less than 100,000/mm-3 may be related to a study that demonstrated that the results of the bleeding time are not prolonged until the platelet count falls below 100,000/mm-3[24]. As discussed earlier, however, the bleeding time is not reliable. The safety of initiating epidural anesthesia when the platelet count is less than 100,000/mm-3 is supported by the results of three retrospective studies [1,25,26]. In the largest study, Beilin et al [1] reviewed the medical records of 15,919 consecutive parturients during a 3-year period. They found 80 women who presented with a platelet count less than 100,000/mm-3, of whom 30 received epidural anesthesia without sequelae. None of these 30 patients had a decreasing platelet count at the time of epidural catheter placement, and none had clinical evidence of bleeding. Five women were denied epidural anesthesia because of decreasing platelet counts and two because of clinical evidence of bruising. There is even one case report of a woman who safely received epidural anesthesia without prior knowledge of a platelet count of 2000/mm-3[27].

Most authors do not define a minimum platelet count below which it is unsafe to perform epidural anesthesia. Each patient must be individualized and the responsible anesthesiologist must weigh the risks versus the benefits. Based on the results of the survey by Beilin et al [7], most anesthesiologists (66% of those in academic practice and 55% of those in private practice) perform epidural anesthesia when the platelet count is between 80,000 and 100,000/mm-3. Below 80,000/mm-3, most anesthesiologists were unwilling to place an epidural catheter.

Practical recommendations

The patient history and physical examination are key components when deciding whether to proceed with regional anesthesia in the parturient with thrombocytopenia. If there is any history of easy bruising or the patient has evidence of any petechiae or ecchymosis, regional anesthesia should not be offered. If the patient has no bleeding history, then general practice is to obtain at least one additional platelet count as close in time to epidural catheter placement as possible to ensure that it is not decreasing further. This testing is especially important for disease processes that are dynamic, such as preeclampsia. The authors do not obtain any tests of platelet function, nor do they have any absolute platelet count cut-off. A patient with a stable platelet count of 50,000/mm-3, as seen in idiopathic thrombocytopenic purpura, is probably at lower risk than one with a platelet count of 75,000/mm-3 that is rapidly decreasing, as seen in preeclampsia.

If the decision is made to proceed with neuraxial anesthesia, a subarachnoid block using a small gauge spinal needle may be preferable to epidural anesthesia. This is not always possible, especially for women in labor who require repeated doses of local anesthetic agents. The epidural catheter should be placed in the midline and analgesia produced with the lowest concentration of local anesthetic agents so as to preserve motor function. The patient should be examined every 1 to 2 hours to assess the extent of the motor block, and these examinations should continue until after the anesthesia has worn off and the catheter has been removed. In this way, if the patient develops a motor block out of proportion to what one would expect or if the anesthesia has a prolonged duration of action, the patient can be assessed immediately with an MRI for the development of an epidural hematoma. Immediate evaluation is necessary because if the patient has an epidural hematoma, an emergent laminectomy and decompression must be performed within 6 to 12 hours to preserve neurologic function [28]. If the patient has an epidural catheter in situ and develops a coagulopathy, the catheter should be removed only after the coagulation status is corrected.

Low molecular weight heparin

The release of LMWH for general clinical use occurred first in Europe in 1987 and then in the United States in 1993. From May 1993 to February 1998, there were more than 40 reports of spinal or epidural hematoma in conjunction with LMWH use in the United States [29]. Emergency laminectomy was performed in 28 patients, 16 of whom suffered permanent paraplegia. The American experience contrasted sharply with the 1992 European data, in which Bergqvist et al [30] showed a greater margin of safety with LMWH. They reviewed 44 controlled studies that involved LMWH and epidural analgesia and were not able to find any reported case of spinal hematoma among 10,000 cases. They estimated that LMWH has been used in conjunction with spinal-epidural anesthesia in almost 1

million patients and there is only one case report of an epidural hematoma [31]. These discrepancies prompted a reevaluation of the risks, benefits, and uses of LMWH in conjunction with neuraxial anesthesia.

Standard, unfractionated heparin is a mixture of linear polysaccharide chains with a molecular weight that ranges from 5000 to 30,000 daltons. Heparin acts as an anticoagulant by binding to antithrombin III and potentiates the inhibition of factors IIa (thrombin), IXa, Xa, XIa, and XIIa. A specific pentasaccharide sequence on the heparin chain has a high-affinity binding site for antithrombin III, but only approximately 30% of the heparin molecule has this sequence. To catalyze inhibition of factor Xa, only the pentasaccharide binding sequence is necessary. To catalyze inhibition of factor IIa, however, a heparin molecule must contain the high-affinity pentasaccharide sequence and an additional chain of at least 13 sugars [32]. Unfractionated heparin is highly sulfated and negatively charged; as a result, it has a great affinity for plasma proteins and vascular matrix proteins and has less than a 30% bioavailability.

Low molecular weight heparin is produced by chemical or enzymatic depolymerization of standard heparin, which produces shorter polysaccharide chains of 13 to 22 sugars and a molecular weight of 4000 to 6000 d [33]. LMWH, has the same anti-Xa activity as standard heparin, but less anti-IIa (thrombin) activity. The concentration of LMWH is referred to in international standards and expressed as anti-Xa units per millimeter. The reduced molecular size leads to lower binding to plasma and endothelial cell proteins. This results in more than 90% bioavailability after subcutaneous injection, a longer plasma half-life (4–6 hours versus 0.5–1 hours for standard heparin), and a predictable and reproducible dose response [34]. Laboratory monitoring is not required. The peak LMWH anti-Xa activity occurs 3 to 4 hours after subcutaneous injection, and 12-hour anti-Xa levels are approximately 50% of peak levels. Low molecular weight heparin excretion is accomplished almost solely by the kidneys. Protamine sulfate is able to neutralize 100% of anti-IIa activity but only 60% to 70% of anti-Xa activity and is not effective at neutralizing LMWH effects.

Pregnancy induces a state of hypercoagulability. Although the incidence of thromboembolic complications is rare, they are a major cause of maternal morbidity. Some parturients require anticoagulant medication during the antepartum period (eg, women with disorders of hemostasis or mechanical heart prostheses or women at high risk for venous thromboembolism). Anticoagulant medication is also used in women with a history of fetal loss related to thrombophilia and hypercoagulable syndromes, such as antithrombin III deficiency, antiphosholipid syndrome, and protein C or S deficiency. Warfarin causes abnormal fetal development and congenital malformations during the first trimester, such as nasal hypoplasia and skeletal dysplasias, and increases the risk of

maternal and fetal hemorrhage when given during the peripartum period [35]. Unfractionated heparin and LMWH do not cross the placenta, are not teratogenic, and are unlikely to cause fetal hemorrhage. LMWH has gained widespread use in pregnancy and has certain advantages over unfractionated heparin. Unfractionated heparin and LMWH have similar hemorrhagic complication rates and antithrombotic efficacy; however, LMWH, unlike unfractionated heparin, does not require laboratory monitoring. There is also less risk of serious complications with LMWH, such as heparin-induced thrombocytopenia and osteoporosis [35].

The release of LMWH for general use in the United States in May 1993 sparked a new challenge for anesthesiologists. Previously, a spinal or epidural hematoma was a rare occurrence, reportedly less than 1 in 150,000 to 220,000 [13]. Enoxaparin, the first LMWH to be approved by the United States Food and Drug Administration, was used for many years in Europe. However, the approved dosing schedule of enoxaparin was 30 mg (3000 U) every 12 hours in the United States, as opposed to 40 mg (4000 U) once daily in Europe. Within 1 year of its introduction in the United States, two cases of epidural hematoma were voluntarily reported through the Med Watch system. The warning section of the drug label was revised and a letter from the manufacturer was issued to practitioners to alert them to the risk of spinal hematoma in patients who undergo neuraxial anesthesia while receiving LMWH. A Food and Drug Administration health advisory also was issued in December 1997 [36].

The actual risk of spinal or epidural hematoma in patients who receive LMWH while undergoing neuraxial anesthesia is difficult to estimate. There are certainly additional, unreported cases. The reported incidences of spinal or epidural hematoma in patients who receive LMWH may be as much as 1 in 3000 for continuous epidural anesthesia and 1 in 100,000 for spinal anesthesia [37]. Of the 40 cases of spinal or epidural hematoma associated with LMWH in conjunction with neuraxial anesthesia, 2 patients received epidural steroid injections, 6 underwent spinal anesthesia, of which 1 was continuous spinal anesthesia, 23 had continuous epidural anesthesia, 6 were unspecified techniques, and 2 had general anesthesia after attempted or failed neuraxial anesthesia. Some of these patients had other risk factors for the development of spinal or epidural hematoma, such as difficult needle placement or administration of antiplatelet or anticoagulant medication. None of these patients was pregnant.

Neuraxial anesthesia can be administered safely to the patient who is receiving LMWH if certain guidelines and precautions are met. The American Society of Regional Anesthesia convened a consensus conference on neuraxial anesthesia in association with anticoagulation in May 1998. A team of clinicians devised recommendations with regard to the administration of neuraxial anesthesia to the patient who receives anticoagulation therapy. The findings are summarized in Box

1, and the full recommendations can be found in the journal *Regional Anesthesia and Pain Medicine*[37] or on the Internet ((http://www.asra.com/items_of_interest/consensus_statements/)).

Box 1:

Summary of the recommendations of the consensus conference convened by the American Society of Regional Anesthesia and Pain Medicine regarding anticoagulants and neuraxial anesthesia and analgesia [20]

1.

The decision to perform a neuraxial block when a patient is receiving LMWH must be made on an individual basis by weighing the risk of spinal hematoma with the benefits of regional anesthesia for a specific patient.
2.

Monitoring of the anti-Xa level is not recommended, because it is not predictive of the risk of bleeding.
3.

Concomitant medications known to potentiate bleeding, such as antiplatelet agents or oral anticoagulants, create an additional risk for the development of spinal hematoma.
4.

If blood is seen during needle or catheter placement, the first dose of LMWH should be delayed for 24 hours.
5.

If a patient is receiving LMWH preoperatively, neuraxial anesthesia should occur at least 10 to 12 hours after the last LMWH dose. Patients who receive high doses of LMWH, such as enoxaparin 1 mg/kg twice a day, require waiting longer, such as 24 hours.
6.

A single-shot spinal technique may be the safest choice for neuraxial anesthesia.
7.

The first dose of LMWH should be given no sooner than 24 hours after neuraxial anesthesia. Indwelling catheters should be removed before initiation of LMWH, and the first dose may be given 2 hours after catheter removal.
8.

If a patient is receiving LMWH and has an indwelling catheter, the catheter should not be removed for at least 10 to 12 hours after the last dose of LMWH.

Summary

The parturient with coagulation defects, whether related to thrombocytopenia or to anticoagulation therapy, presents a unique challenge to the anesthesiologist. The risk of spinal or epidural hematoma in these patients has not been quantified fully but is a factor that one must consider on a case-by-case basis in determining whether neuraxial anesthesia is appropriate for the parturient. Following the guidelines set forth in this article should help reduce the risk of spinal or epidural hematoma without sacrificing the quality of care provided to patients.

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