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# The Anticoagulated Parturient

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Neuraxial analgesia and anesthesia are routinely administered to the parturient. A devastating, albeit rare, complication of neuraxial anesthesia is spinal or epidural hematoma, and primarily occurs in patients with disorders of hemostasis. A parturient with a clinically active coagulation disorder, or someone with a history of easy bruising and/or bleeding, is considered to have an absolute contraindication to regional anesthesia. However, many areas of controversy exist and this is especially true in patients with thrombocytopenia and those receiving 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, the laboratory tests available to test platelet function, and to provide recommendations as to the lowest platelet count that is acceptable for neuraxial anesthesia. In addition, an increasing number of patients are receiving anticoagulant medications during pregnancy and low molecular weight heparin (LMWH) is one of these agents. The role of LMWH during pregnancy and its implications for labor analgesia will also be 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 an epidural anesthetic. However, approximately 7% of all parturients will present

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with a platelet count  $<150,000 \text{ mm}^{-3}$ , and 0.5% to 1% will present with a platelet count  $<100,000 \text{ mm}^{-3}$ .<sup>1</sup>

An epidural or spinal hematoma can be a catastrophic complication, which can lead to permanent paralysis. In 1988, Cousins and Bromage<sup>2</sup> recommended that one should not place an epidural catheter if the platelet count is less than  $100,000 \text{ mm}^{-3}$ . Recently, their recommendation has been challenged, primarily because thrombocytopenia occurs frequently during pregnancy<sup>1</sup> and neuraxial anesthesia is safer than general anesthesia for the parturient.<sup>3</sup> 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<sup>3</sup> 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 women who had regional anesthesia. There is an increasing trend to use 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. Furthermore, if the woman later requires a cesarean delivery, perhaps emergently, the anesthesiologist may then be forced to administer an anesthetic under less than optimal conditions.

Clotting can be thought of as occurring in 2 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 allowing platelets to adhere to the vessel wall. This adhesion leads to activation and degranulation of platelets with release of adenosine 5-diphosphate (ADP), serotonin, and thromboxane, which then leads to platelet aggregation. Further aggregation leads to the formation of a platelet plug. This 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 1 of 3 causes: hypertensive disorders such as preeclampsia, gestational thrombocytopenia, or idiopathic thrombocytopenic purpura (ITP). When evaluating the parturient with thrombocytopenia, there are 2 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 rapidly change 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 parturient with thrombocytopenia is difficult to evaluate with standard laboratory tests because both platelet quantity and quality must be assessed. Tests of platelet function have been criticized for being difficult to perform, for lacking reproducibility, and being of questionable clinical relevance. The ideal test should be easy to perform, inexpensive, would not require specialized equipment and the results could be reproduced and correlated with outcome. Bedside tests of coagulation include the bleeding time, thromboelastography (Haemoscope Corporation, Skokie, IL), and newer tests such as the platelet function analyzer, PFA-100 (Dade Behring, Newark, DE).

The bleeding time is a simple bedside test that evaluates both 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. However, the bleeding time is no longer recommended to determine the safety of epidural catheter placement because bleeding at the test site does not necessarily reflect the risk of bleeding at other sites,<sup>4,5</sup> and there is also wide observer variation.<sup>6</sup> O'Kelly et al<sup>6</sup> asked 12 observers to assess the bleeding time on 5 separate volunteers. The reliability of the measurements obtained was poor among the 12 observers and the authors concluded that the test is unreliable. Although no longer recommended, a survey by Beilin et al<sup>7</sup> 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 a neuraxial anesthetic in the parturient with thrombocytopenia.

The thromboelastogram (TEG) 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. The maximum amplitude (MA) has been found to correlate best with platelet function.

Orlikowski et al<sup>8</sup> measured platelet counts, TEG parameters, and bleeding time in healthy pregnant women and in those with preeclampsia. They found that the MA remained normal (53 mm) until the platelet count decreased to less than  $54,000 \text{ mm}^{-3}$  (95% confidence limit  $40\text{--}75,000 \text{ mm}^{-3}$ ). On the basis of their study, they suggested that a platelet count of  $75,000 \text{ mm}^{-3}$  should be associated with adequate hemostasis. However, there is no clinical evidence that a normal MA correlates with safe epidural analgesia.

The PFA-100 is an intriguing test because it is specific to platelet function, the primary disorder in the parturient with preeclampsia. The machine simulates the *in vivo* hemostatic mechanism of platelet function by accelerating citrated whole blood through a small,  $150 \mu\text{m}$ , aperture cut into a collagen membrane. The collagen membrane is coated with 1 of 2 platelet activators, epinephrine or ADP. The time taken for the aperture to close is called the closure time (CT). 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 disease.<sup>9</sup> However, Beilin et al<sup>10</sup> were unable to find a correlation between the CT and the platelet count or between the CT and the MA in the parturient.

The overall risk of epidural or spinal hematoma after neuraxial anesthesia is in the range of 1:150,000 to 220,000.<sup>11</sup> Vandermeulen et al<sup>11</sup> reviewed the literature and found 61 cases of anesthesia-related spinal hematoma. Most (68%) occurred in patients with coagulopathies, and 75% of all cases had an epidural rather than a spinal anesthetic. Of those who received an epidural anesthetic, 88% had an epidural catheter inserted and almost 50% of those patients developed an epidural hematoma after catheter removal.

We are aware of 10 reports in the literature of neuraxial (spinal or epidural) hematoma occurring in parturients. In 3 of these cases, the diagnoses were made clinically, and the symptoms resolved spontaneously.<sup>12–14</sup> 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.”<sup>15</sup>

Three of the 10 parturients had anatomic abnormalities of their spines, which were not appreciated before the initiation of labor analgesia. In 2 cases, the patients were reportedly healthy, but both were later found to have a spinal ependymoma, which are unpredictable and rare occurrences.<sup>16,17</sup> Another patient with neurofibromatosis developed mild neurologic symptoms postpartum and a magnetic resonance imaging (MRI) revealed a small epidural hematoma; the symptoms resolved the next day without intervention.<sup>18</sup>

In another 2 of the 10 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.<sup>19,20</sup> One of these 2 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 of 27.7 seconds and partial thromboplastin time of 59.1 seconds.<sup>20</sup> The second woman presented with preeclampsia and had a history of a lupus anticoagulant.<sup>19</sup> Her preoperative laboratory tests revealed a normal platelet count of  $425,000 \text{ mm}^{-3}$ , prothrombin time of 10.5 seconds, and bleeding time of 3 minutes. Her partial thromboplastin time was elevated at 49 seconds but this was attributed to a lupus anticoagulant, so the decision was made to proceed with an epidural anesthetic 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  $71,000 \text{ mm}^{-3}$ .<sup>21</sup> The patient had an epidural anesthetic 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. The patient recovered 72 hours later. Whether the 4 mL of epidural blood 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  $<100,000 \text{ mm}^{-3}$  may be related to a study demonstrating that the results of the bleeding time are not prolonged until the platelet count falls below  $100,000 \text{ mm}^{-3}$ .<sup>22</sup> However, we are now aware that the bleeding time is not reliable. The safety of initiating an epidural anesthetic when the platelet count is  $<100,000 \text{ mm}^{-3}$  is supported by the results of 3 retrospective studies.<sup>1,23,24</sup> In the largest study, Beilin et al<sup>1</sup> reviewed the medical records of 15,919 consecutive parturients during a 3-year period. They found 80 women who presented with a platelet count  $<100,000 \text{ mm}^{-3}$ , and 30 of these women received an epidural anesthetic without sequelae. None of these 30 women had a decreasing platelet count at the time of epidural catheter placement and none had clinical evidence of bleeding. Five women were denied an epidural anesthetic because of decreasing platelet counts and 2 because of clinical evidence of bruising. There is also 1 case report of a woman who safely received an epidural anesthetic without prior knowledge of a platelet count of  $2000 \text{ mm}^{-3}$ .<sup>25</sup>

Most authors do not define a minimum platelet count below which it is unsafe to perform an epidural anesthetic. Indeed, each patient must be individualized and the responsible anesthesiologist must weigh the risks versus the benefits. On the basis of the results of the survey by Beilin et al,<sup>7</sup> most anesthesiologists (66% of those in academic practice and 55% of those in private practice) will perform an epidural anesthetic when the platelet count is between 80,000 and 100,000  $\text{mm}^{-3}$ . Below 80,000  $\text{mm}^{-3}$ , most were unwilling to place an epidural catheter.

## ■ Practical Recommendations

The patient history and physical examination are key components when deciding whether to proceed with a regional anesthetic 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 our 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 is especially important for disease processes that are dynamic, such as preeclampsia. We do not obtain any tests of platelet function nor do we have any absolute platelet count cut-off. A patient with a stable platelet count of 50,000  $\text{mm}^{-3}$ , as seen in ITP, is probably at lower risk than one with a platelet count of 75,000  $\text{mm}^{-3}$  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 will require repeated doses of local anesthetic. The epidural catheter should be placed in the midline and analgesia produced with the lowest concentration of local anesthetics, 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 anesthetic 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 anesthetic has a prolonged duration of action, the patient can be immediately assessed with 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.<sup>26</sup> 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.<sup>11</sup>

## ■ 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 over 40 reports of spinal or epidural hematoma in conjunction with LMWH use in the United States.<sup>27</sup> Emergency laminectomy was performed in 28 patients, and 16 of these patients suffered permanent paraplegia. The American experience contrasted sharply with the 1992 European data where Bergqvist et al<sup>28</sup> showed a greater margin of safety with LMWH. They reviewed 44 controlled studies involving LMWH and epidural analgesia and were not able to find any reported case of spinal hematoma among 10,000 cases. Furthermore, they estimated that LMWH has been used in conjunction with spinal/epidural anesthesia in almost 1 million patients and there is only 1 case report of an epidural hematoma.<sup>29</sup> These discrepancies prompted a reevaluation of the risks, benefits, and uses of LMWH in conjunction with neuraxial anesthesia.

Standard, unfractionated heparin (UH) is a mixture of linear polysaccharide chains, with a molecular weight that ranges from 5000 to 30,000 d. 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 about 30% of the heparin molecule has this sequence. To catalyze inhibition of factor Xa, only the pentasaccharide binding sequence is necessary. But to catalyze inhibition of factor IIa, a heparin molecule must contain both this high-affinity pentasaccharide sequence and an additional chain of at least 13 sugars.<sup>30</sup> UH 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 30% bioavailability.

LMWH 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.<sup>31</sup> LMWH has the same anti-Xa activity as standard heparin with less anti-IIa (thrombin) activity. The concentration of LMWH is referred to in international standards and expressed as anti-Xa units per milligram. The reduced molecular size leads to lower binding to plasma and endothelial cell proteins. This results in greater than 90% bioavailability after subcutaneous injection, a longer plasma half-life (4 to 6 h vs. 0.5-1 h for standard heparin) and a predictable and reproducible dose response.<sup>32</sup> 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. LMWH 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 therefore 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, for example those with disorders of hemostasis or mechanical heart prostheses, or those at high risk for venous thromboembolism. Additionally, anticoagulant medication is used in women with a history of fetal loss related to thrombophilia and hypercoagulable syndromes, such as antithrombin III deficiency, antiphospholipid 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.<sup>33</sup> UH 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 UH. Both UH and LMWH have similar hemorrhagic complication rates and antithrombotic efficacy; however, LMWH, unlike UH, does not require laboratory monitoring. Also, there is less risk of serious complications with LMWH, such as heparin-induced thrombocytopenia and osteoporosis.<sup>33</sup>

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 rather rare occurrence, reportedly less than 1 in 150,000 to 220,000.<sup>11</sup> Enoxaparin, the first LMWH to be approved by the United States Food and Drug Administration (FDA), had been 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, 2 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 undergoing neuraxial anesthesia while receiving LMWH. An FDA Health Advisory was also issued in December 1997.<sup>34</sup>

The actual risk of spinal or epidural hematoma in patients receiving 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 receiving LMWH may be as much as 1 in 3000 for continuous epidural anesthesia and 1 in 100,000 for spinal anesthesia.<sup>35</sup> 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 safely administered to the patient receiving LMWH if certain guidelines and precautions are met. The American Society of Regional Anesthesia (ASRA) formed a consensus committee on neuraxial anesthesia in association with anticoagulation on May 2 to 3, 1998. The committee reconvened for a second consensus conference in 2002. This team of clinicians devised recommendations with regard to the administration of neuraxial anesthesia to the patient receiving anticoagulation therapy. The findings are summarized in Table 1 and the full recommendations can be found in the journal, *Regional Anesthesia and Pain Medicine*<sup>35</sup> or on the Internet at the following URL address [http://www.asra.com/items\\_of\\_interest/consensus\\_statements/](http://www.asra.com/items_of_interest/consensus_statements/).

In 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

**Table 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<sup>35</sup>

- (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 h.
- (5) If a patient is receiving LMWH preoperatively, neuraxial anesthesia should occur at least 10 to 12 h after the last LMWH dose. Patients receiving high doses of LMWH, such as enoxaparin 1 mg/kg twice a day, will require waiting longer, such as 24 h.
- (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 h after neuraxial anesthesia. Indwelling catheters should be removed prior to initiation of LMWH, and the first dose may be given 2 h 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 h after the last dose of LMWH.

hematoma in these patients has not been fully quantified, but is nevertheless a factor that one must consider on a case-by-case basis in determining whether a neuraxial anesthetic 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 our patients.

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