Anesthetic Management of Preeclampsia with HELLP Syndrome

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Preeclampsia has been described in the literature for decades as a collectivity of hemolysis, he patic dysfunction, and low platelets in pregnancy. However, it was not until 1982 when Weinstein coined for it the acronym HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets)[1]. The pathophysiology of preeclampsia especially HELLP syndrome have revealed a disorder characterized by hepatic endothelial disruption followed by platelet activation, aggregation, and consumption resulting in distal ischemia and death of hepatocytes[2]. Later, Sebai et al[3] defined laboratory abnormality sufficient for the diagnosis of each element of the syndrome: hemolysis by an abnormal peripheral smear, elevated bilirubin > 1.2 mg/dL, or elevated lactate dehydrogenase (LDH) > 600 U/L, elevated liver enzymes by an aspartate aminotransferase (AST) > 70 U/L, lactate dehydrogenase (LDH) > 600 U/L, and low platelets which is defined as platelet count ≤ 100,000/mm^3. Martin et al[4] also classified HELLP syndrome with platelets below 50,000/mm^3 as class I, between 51,000-100,000/mm^3 as class II and between 110,000-150,000 mm^3 as class III. However, the pathophysiology is dynamic, i.e, it can produce a number of outcomes, whether the patient has evidence of thrombocytopenia and elevated liver function tests alone or whether schistocytes are present in the blood smear, the serum bilirubin is elevated or other abnormalities such as coagulopathy or renal insufficiency have unfolded. With greater involvement of the endothelium of the liver in preeclampsia, more red cells are hemolyzed and more hepatic ischemia resulted in higher bilirubin levels and impaired coagulation tests. Therefore, some patients may be classified as partial HELLP syndrome, ELLP syndrome, or class III HELLP syndrome. Furthermore, we may also come across EL or HEL syndrome. Van Pampus et al[5] found that 10% of women with ELLP syndrome were identified as having serious complications including eclampsia, cerebral ischemia, and abruptio placenta compared with 24% rate for women with true HELLP. However, once severe preeclampsia appears, it can have remarkable end organ involvement, adverse renal, central nervous system, and pulmonary complications can be seen and needed appropriate management. The attempt to differentiate HELLP versus ELLP versus EL or HEL syndrome is of limited value when attempting to treat patients with severe preeclampsia with hepatic involvement. The diagnosis of HELLP syndrome, however, depends on laboratory parameters alone, although the findings of preeclampsia such as hypertension and proteinuria help rule out other similar diseases. A complete blood count including peripheral blood smear, platelet count, coagulation studies and liver function tests including serum AST, LDH, bilirubin, glucose and creatinine can help fulfill the criteria. Since it is not easy to evaluate peripheral smear, especially at night, LDH value is used to indicate hemolysis, although it also reflects hepatocyte destruction.

Differential diagnosis may be needed in patients with nausea vomiting and epigastric pain. However, a pregnant woman in her late second or early third trimester with right upper quadrant pain and hepatic dysfunction should be considered as having HELLP syndrome Although severe hypertension (systolic blood pressure (SBP) ≥ 160 and diastolic blood pressure (DBP) ≥ 110 mmHg) is not a constant finding in HELLP syndrome; concomitant hypoglycemia, coagulopathy, elevated ammonia levels, and renal dysfunction are associated with acute fatty liver in pregnancy. Cerebral dysfunction, fever and rash may be a part of thrombotic thrombocytopenic purpura. Hemolytic uremic disease is usually related to infection and mostly develops in the postpartum period. Exacerbation of SLE with nephritis can also mimic severe preeclampsia.

Although the involvement in hepatic and renal vessels is most common, other vessels included the cerebral, cardiac vessels may be involved, causing concomitant eclampsia, myocardial dysfunction and pulmonary edema.

Management: The patients should be immediately hospitalized in tertiary care centers. They should be managed as having severe preeclampsia including magnesium sulfate for seizure prophylaxis, antihypertensive therapy to keep the SBP < 160 and/or DBP < 105 mmHg before proceeding to delivery. The first priority is to assess and stabilize the maternal condition including coagulation abnormalities. Hydralazine 5 mg bolus can be used and repeated as needed, or every 15 minutes at the maximum dose of 20 mg/hour. If hydralazine is not effective or should the side effects such as headache or tachycardia develop, labetalol 20 to 40 mg IV every 10-15 minutes for a maximum of 220 mg/hour, or nefedipine 10-20 mg orally every 30 minutes should be used. Magnesium sulfate can be given at 6 g as a loading dose over 20 minutes followed by a maintenance dose of 2 g/hour by IV infusion.

Steroid treatment in HELLP syndrome: Several studies have demonstrated that dexamethasone improves the

laboratory values in HELLP syndrome. The mechanism of which is still unknown but steroids may minimize the degree of endothelial cell damage; hence, decrease the death rate of hepatocytes and platelet consumption. Other than using glucocorticoid to improve fetal lung maturity, it can increase maternal platelet count before delivery.[6,7] They also observed significantly increased use of regional anesthesia in women who were exposed to glucocorticoid for 24 hours, compared to the group without steroid treatment. Regional anesthesia has been shown to avoid complications of exacerbated hypertension, aspiration, and failure of intubation attributable to general anesthesia in these patients.

In case of preterm patients, at < 34 weeks of gestation, glucocorticoid is used for the benefit of fetal maturation and maternal stabilization. For women at ≥ 34 weeks of gestation, glucocorticoid is used on maternal indications such as epigastric pain, severe headache or more pronounced laboratory changes. Delivery is usually scheduled in 24-48 h after the diagnosis of HELLP syndrome, once the maternal status is stabilized and the fetus has obtained benefit from the steroid treatment. O'Brien et al6 assessed the beneficial effects of glucocorticoid administration on the rate of regional anesthesia in patients with HELLP syndrome. Their regimens include dexamethasone 6 mg IV every 6 hour for four doses, or betamethasone 12 mg IM every 12 hour for two doses or high dose of dexamethasone, 10 mg IV every 6 hour for two doses, then 6 mg every 6 hour for two doses. The patients would be considered candidates of regional anesthesia if the platelet count was > 90,000/mm^3, with no precipitous drop in the platelet count or no evidence of spontaneous bleeding. The platelet counts at delivery of those who were exposed to steroids and those who were not were: 88,000±40,000/mm^3 and 72,000±20,000/ mm^3, respectively; p<0.093. In thirty-seven women who had platelet count of < 90,000/ mm^3, 0% in the untreated group (0/11) versus 42% (11/26) in the steroid group received regional anesthesia; p<0.015. The need for general anesthesia in cesarean delivery also decreased in the treated group (46%, 7/15), as compared to the untreated group (100%, 8/8); p<0.019. Rose et al8 also reviewed the effects of high doses steroid, 10 mg dexamethasone IV every 12 hour until delivery and another two doses after delivery, then 5 mg every 12 hour for two times. Their data suggested the benefit to those patients presenting with the platelet counts of less than 75,000 mm3 that they can be more eligible to receive either spinal or epidural anesthesia. However, according to a prospective survey by Auroy et al9, the estimated incidences of spinal and epidural hematoma would be 1: 104,038 and 1:55,613, respectively[10].

Transfusion:

Platelet transfusions are indicated in all patients with HELLP syndrome whose platelet count is less than 20,000 mm^3 or in the presence of significant bleeding from punctured sites, wound or echymosis. Repeated platelet transfusion may not be necessary because the consumption occurs rapidly and the effect is transient. Transfusion of six to ten units of platelets before intubating the patient for cesarean section is suggested. Red cells and fresh frozen plasma may also be needed in patients with more severe coagulopathies. Rupture of a subscapular hematoma is particularly concerning because it can lead to massive hemorrhage. Patients typically report right upper quadrant pain. Surgical repair has been recommended for hepatic hemorrhage. Resuscitation should consist of massive transfusions of blood, correction of coagulopathy with fresh frozen plasma and platelets, and immediate laparotomy. O'Brian et al recommend 30 units of packed red cells, 20 units of fresh frozen plasma, 30 to 50 units of platelets, and 20 to 30 units of cryoprecipitate be made available if rupture of a subcapsular hematoma is suspected[11].

Evaluation of platelet function in preeclampsia:

Platelets play an important role in hemostasis system by aggregating and forming plugs, and the entire coagulation cascade occurs on the platelet membrane. Tests of platelet function include bleeding time test, thromboelastography, and aggregometry, or flow cytometry.

In addition to hypertension, preeclamptic women may have reduced platelet count and function. It has been shown that when the platelet count is less than 100,000/ mm^3, other hemostatic abnormality such as prolonged prothrombin time (PT) and partial thromboplastin time (PTT), and reduced fibrinogen concentration may also be presented.

Bleeding time test:

Previously, it was recommended to perform a bleeding time before regional anesthesia if the platelet count was < 100,000 mm^3. If the bleeding time was abnormal, regional anesthesia was considered contraindicated[12]. However, this test is no longer considered useful to determine the safety of epidural catheter placement because it does not necessarily reflect the risk of bleeding at other locations13and having a wide observer variation[14].

Thromboelastography (TEG):

TEG measures all phases of blood coagulation (interaction between platelet phospholipid and coagulation factors) and fibrinolysis. It has been suggested as a reliability test for platelet function. However, TEG does not measure the interaction between the damaged vessel wall and the platelets. Orlikowski et al[15], studied 40 preeclamptic and eclamptic patients and found that 14% of them had platelet count < 100,000/mm^3. They also found a strong correlation between TEG variables (k time and MA) with platelet count. However, they found no correlation between the bleeding time and thrombocytopenia. A Maximum Amplitude (MA) of 53 which is the lowest normal limit for normal pregnancy correlated with a platelet count of 54,000/ mm^3 (95% CI = 40,000 - 75,000/ mm^3). So, they concluded that although their sample size was small, a platelet count of 75,000/mm^3 would be associated with adequate hemostasis.

Sharma et al[16] studied by using TEG and found that 30% (34 of 114) of severe preeclamptic patients had platelet count < 100,000/mm^3, as compared to 3% in mild preeclamptic patients and 2% in healthy pregnant women. Ten severe preeclamptic patients with platelet count < 65,000/mm^3 who did not have epidural anesthesia, had a maximum amplitude (MA) < 54 mm (the lowest limit of maximum amplitude in healthy pregnant women enrolled in this investigation). Every parturient with a platelet count >75,000/mm^3 had a normal MA (>54 mm). However, in both studies of TEG and platelet counts, few patients with platelet count <75,000/mm^3 had regional anesthesia. There is less evidence that a normal thromboelastogram can determine the safety of epidural anesthesia. Therefore, it is difficult to conclude that the reliability of TEG can predict the development of epidural hematoma.

The Platelet Function Analyzer (PFA-100):

PFA-100 evaluates platelet function by measuring the time required for whole blood to occlude an aperture in a membrane coated with collagen and the platelet agonists, epinephrine (PFA- EPI), or adenosine diphosphate (PFA-ADP), called closure time[17]. Vincelot et al[18], studied platelet function using PFA-100 in patients with thrombocytopenia associated with preeclampsia and found a correlation between platelet numbers and PFA-ADP closure time (normal range 71 - 118 seconds) especially when the platelet count was less than 50,000/mm^3. This test takes about 7 min; however, false negative and false positive are also seen.

Aggregometry:

Aggregometry measures the ability of platelets to aggregate in response to specific protein agonists, and flow cytometry measures platelet activation and function which both may be a gold standard test. However, neither test is a practical clinical test, as both require too much time and the technical expertise.

However, the main disadvantage of all laboratory platelet function test is that they do not measure the interaction between platelet and the vascular endothelium.

Delivery:

Primary cesarean section was performed in 73% of patients presenting with HEELP syndrome before 34 weeks of gestation; substantial thrombocytopenia typically mandated general anesthesia. Only 13% of these patients at less than 30 weeks of gestation were vaginally delivered [11].

Anesthesia:

Historically, most of these women have undergone general anesthesia for cesarean delivery. However, general anesthesia in this population is risky due to exacerbation of hypertension, aspiration, or failed intubation. The lower limit of platelet count associated with safe regional blockage has been questioned. Regional anesthesia itself is not without any risk of epidural hematoma. About 5% of patients with HELLP syndrome demonstrate laboratory evidence of impaired clotting function[11], and spontaneous bleeding is uncommon until the platelet count falls below 40,000/ mm^3.

Evidences support the use of spinal anesthesia in severe preeclampsia

Anesthesia for cesarean delivery in severe preeclampsia has been changed dynamically during the past 20 years. Although the maternal mortality from general anesthesia was proved to be 7-fold higher than from regional anesthesia, both epidural and spinal anesthesia were suggested to be avoided in women with preeclampsia[19]. Although the potential risks from airway events may be even greater in preeclamptic women due to increased airway edema and heightened cardiovascular responses to laryngoscopy and intubation[20]. Later, it has been demonstrated the relatively safety and value of well managed incremental epidural anesthesia in preeclamptic women requiring cesarean section. Despite its simplicity, speed and cost effectiveness, there is common belief (without evidence support) that the sudden and extensive sympathetic blockage by spinal anesthesia will result in a greater incidence and severity of hypotension. However, there is a growing support for the use of spinal anesthesia in these patients. A small prospective randomized study of preeclamptic patients did not find significant difference of blood pressure between spinal and epidural anesthesia[21]. A retrospective study done by Hood and Curry[22] found no difference in the incidence of hypotension after spinal or epidural anesthesia in cesarean deliveries with severe preeclampsia. Another recent retrospective study done by Chiu et al[23] also showed that the decrease in blood pressure was similar after spinal and epidural anesthesia. The use of intravenous fluids and ephedrine were also comparable in the two anesthetic groups. Recently, a large prospective study done by Visalyaputra et al[24] showed that, although the incidence of hypotension was higher (51% vs. 23%) and the ephedrine requirement was more (median = 6 vs. 0 mg) in the spinal group than in the epidural group, the difference in the mean lowest blood pressure was small (mean difference =10, 95%; CI = 4-17 mmHg). There was only a brief period of significant hypotension in both spinal and epidural groups (median =1 and 0 min). The neonatal outcomes assessed by Apgar scores and the umbilical arterial blood gas analyses were similar in both groups. The adverse neonatal outcomes (5 min Apgar score <7, and the umbilical arterial blood pH < 7.20) were found only in two premature newborns (weigh < 1500 gm) who were born without maternal hypotension after regional anesthesia. Aya et al[25], also compared hemodynamic changes from spinal anesthesia for cesarean delivery between healthy and preeclamptic parturients in their prospective and randomized studies. They found that despite receiving a smaller fluid volume (1653 ± 221 ml vs. 1895 ± 150 ml) and a larger bupivacaine dose (10.5 ± 0.9mg vs. 10.0 ± 0.7 mg), the severely preeclamptic patients had, the less the frequency of the incidence of clinical hypotension (16% vs. 53,3%), which was less severe and required less ephedrine. The risk of hypotension was almost six times less in severely patients than that in healthy patients. Dyer et al[26] compared between general and spinal anesthesia in their randomized prospective study in 70 preeclamptic patients with a nonreassuring fetal heart trace. They found that the hemodynamic change remained within the acceptable range in both groups. One min Apgar score was lower in the general group but 5 min Apgar score was similar. Umbilical blood pH was lower (7.20) in the spinal group as compared with 7.23 in the general group. Although these numbers were statistical significant different, they were within normal range. All these retrospective and prospective studies are in the same direction which support the use of spinal anesthesia for cesarean section in severely preeclamptic patients.

Evidences support the use of spinal anesthesia in severe preeclampsia with thrombocytopenia is only from case reports

A decreasing platelet count is considered a contraindicated to neuraxial blockage, especially in a dynamic conditions such as preeclampsia and ITP. A physical examination of the patient should include looking for evidence of bruising and bleeding at venepuncture sites. Consumptive coagulopathy associated with placental abruption and other condition must be ruled out. A patient's entire clinical presentation should be taken into account when deciding on the appropriate anesthetic technique.

The safe lower limit of platelet count for regional anesthesia is unknown. The incidence of thrombocytopenia during pregnancy is about 0.5-0.8%. Most anesthesiologist[27] (66% of those in academic practice and 55% of those in private practice) would place an epidural when

the platelet count is 80,000-100,000/mm^3. Rolbin et al[28] reviewed the platelet counts of 2,204 parturients and found three parturients with a platelet count < 100,000/ mm^3 who received epidural anesthesia without neurological sequelae. Rasmas et al[29] reviewed the record of 2,929 parturients for thrombocytopenia. They found twenty-four women whose platelet count was < 100,000/mm^3. Five of these twenty-four patients had epidural catheter placement when the platelet count was < 100,000/mm^3. Beilin et al[30] reported in larger series of parturients who had an epidural anesthetic placed without complication. Thirty patients had the platelet count between 69,000-98,000/ mm^3 at the time of the epidural catheter placement and six of them were preeclamptic patients.

To deny regional anesthesia to preeclamptic patient because of the low value of the platelet count is not only detrimental to her health but it also gives her a chance to take risk of general anesthesia with difficult airway.

It is suggested that if the parturient presents in labor with a low platelet count (close to 100,000/mm^3), we should obtain at least one additional platelet count at the time which is close to epidural placement as much as possible to assure that it is not decreasing further[28]. It is also suggested to use the lowest concentration of local anesthetic necessary to produce analgesia while preserving motor function. The patient should be observed every 1-2 hour to assess the motor block until after the catheter has been removal. If the patient has prolonged motor block or prolonged analgesia, the patient should be immediately assessed using computed tomography or magnetic resonance imaging. If the patient has an epidural hematoma, an emergency laminectomy and decompression should be done within 6-12 h to prevent permanent neurological dysfunction.

However, the combined sample size from all these retrospective study is insufficient to provide any meaningful 95% confidential levels. Large prospective studies with estimated sample size of > 200,000 are required to definitely determine whether it is safe to place an epidural or spinal anesthetic in patients with a platelet count < 100,000/ mm^3.

When considering regional anesthesia, associated with patients with thrombocytopenia, spinal anesthesia may be a safer option. Careful monitoring of the patient in the postpartum period to detect early signs and symptoms of an epidural hematoma should be undertaken.

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