Summary

We describe the use of thrombelastography in HELLP syndrome (Haemolysis, Elevated Liver Enzymes, Low Platelets). It differentiated between two possible causes of significant haemorrhage and revealed an accompanying underlying fibrinolysis. This allowed specific therapy to be directed at both abnormalities and, we believe, helped prevent this patient from undergoing radical surgery to curb blood loss. (Br. J. Anaesth. 1995; 74: 464-468)

Key words


Case report

A 22-yr-old Asian woman was admitted to another hospital at 38 weeks' gestation in her second pregnancy with nausea, vomiting and jaundice. There was no significant past medical history. She was subsequently found to have elevated hepatic enzyme concentrations: serum bilirubin 86 μmol litre⁻¹ (normal range 5-17 μmol litre⁻¹), aspartate transaminase 430 u. litre⁻¹ (5-40 u. litre⁻¹) and alkaline phosphatase 1020 u. litre⁻¹ (35-130 u. litre⁻¹) (fig. 1), and a platelet count of 122 x 10⁹ litre⁻¹ (fig. 2).

Two days after admission, the decision was made to deliver the baby and therefore she underwent induction of labour and forceps delivery under extradural analgesia. After delivery arterial pressure was increased, with diastolic pressures of 110-120 mm Hg and she was confused. Haematology results at this time (fig. 2) showed a platelet count of 99 x 10⁹ litre⁻¹ and the international normalized ratio (INR) was 2.3 (0.9-1.2). She was given hydralazine i.v. and transferred to the intensive therapy unit (ITU) for management of impending renal failure. On return to the ITU she continued to bleed heavily

Management consisted of haemodialysis, transfusion of blood to maintain a haemoglobin concentration of approximately 10 g dl⁻¹, coagulation factors in the form of fresh frozen plasma (FFP 10 u. and 3 litre of plasma exchange), cryoprecipitate (5 u.), platelets (17 u.), antibiotics and antiviral agents. Seven hours after her first session of haemodialysis and plasma exchange, coagulation had deteriorated further with a PT of 25.2 s, APTT 147 s, fibrinogen 1.8 g litre⁻¹ and FDP 20-40 mg litre⁻¹.

During the first 24 h of intensive care she had heavy vaginal bleeding and was returned to the operating theatre for evacuation of retained products of conception and packing of the uterus. However, on return to the ITU she continued to bleed heavily and arrangements were made for another examination under anaesthesia and hysterectomy was contemplated. The first thrombelastograph (fig. 3) was then performed (TEG 1; fig. 4); this was a flat trace, suggestive of either severe coagulopathy or an effect of heparin, or both. This was following a 3-litre plasma exchange, FFP 14 u. and platelets 6 u. (PT 15 s, APTT 39 s). Heparin 500 u. h⁻¹ had been used during haemodialysis and TEG 1 was performed towards the end of dialysis. Prostacyclin was also being used in the management of renal failure. A celite-activated sample of whole blood was then analysed [1], the celite substituting as a contact activator of coagulation, thus making the "r" time of the TEG equivalent to the activated clotting time (ACT). The resulting trace (TEG 2) indicated that at least part of the cause of TEG 1 was an effect of heparin added to the possible presence of endogenous heparinoids [2, 3]. She was therefore given

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Thrombelastography reveals two causes of haemorrhage in HELLP syndrome

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protamine 50 mg i.v. This produced TEG 3 with normal r and "rk" times and a good alpha angle. This now revealed a degree of fibrinolysis evidenced by a too rapidly reducing width of trace [4]. She was therefore given an infusion of aprotinin [5], with a bolus dose of 2 million u. followed by 500 000 u. h⁻¹.

Overnight, vaginal blood loss decreased markedly. Another celite-activated trace (TEG 4) later that day, after a 2.4-litre plasma exchange and 15 u. of platelets, showed improved clotting factor and platelet activity (PT 16 s, APTT 33 s), although slightly prolonged r and rk times, reduced alpha angle and maximum amplitude were still present. It also revealed that fibrinolysis was controlled with aprotinin which was continued until day 10.

She continued to have plasma exchanges and on day 14 the celite-activated TEG (TEG 5) and native whole blood (TEG 6), showed improved, but still deficient, clotting factor and platelet function and no further fibrinolysis. There was however another episode of haemorrhage from a wound drain and the perineal haematoma and blood film again had features of haemolysis. She was given 6 u. of blood over 2 days with another plasma exchange and 12 u. of platelets (PT 16 s, APTT 39 s, platelets 67 x 10⁹ litre⁻¹ FDP 40–80 mg litre⁻¹).

On day 15 renal function improved and after removal of the vaginal pack, the trachea was extubated. TEG 7 was normal and 2 days later she was transferred back to the renal unit.

Discussion

HELLP syndrome (Haemolysis, Elevated Liver Enzymes, Low Platelets) was first described in 1954 by Pritchard and colleagues [6] in association with pre-eclampsia, although the acronym was not used. Two of their three patients died and they proposed that the coagulation and liver enzyme abnormalities were associated with pre-eclampsia and that an immunological process may be involved.

In 1982 Weinstein [7] first coined the term HELLP syndrome. He suggested that these ab-
contraindicated [10], fetal thrombocytopenia, prematurity [13].

...to placental abruption, intrauterine asphyxia and up to 24% [10] and perinatal mortality 33% related not were at increased risk of developing pulmonary manifestations ranges from a few hours to 6 days, with severe pre-eclampsia [10, 11]. The onset of labor and dysfunction maximal on day 1 post-partum. Using the simpler criteria of decreased platelets, low fibrinogen and FDP > 40 mg litre⁻¹, Sibai and colleagues [13] found DIC present in 38% of patients with this syndrome. FDP are non-specific unless greater than 40 mg litre⁻¹ but 15% of patients with DIC have concentrations < 40 mg litre⁻¹. FDP also have a long half-life of 5–72 h and so do not always reflect current coagulation status [15].

Figure 4   Examples of thrombelastograph (TEG) traces in our patient (see text for details). INR = International normalized ratio, PT = prothrombin time, APTT = activated partial thromboplastin time.

HELLP syndrome is thought to complicate 0.3% of all pregnancies and between 4 and 12% of those with severe pre-eclampsia [10, 11]. The onset of manifestations ranges from a few hours to 6 days, with the majority developing within 48 h of delivery. Seventy-nine percent of patients had evidence of pre-eclampsia before delivery, but the 21% who did not were at increased risk of developing pulmonary oedema and acute renal failure [10, 12]. Maternal and fetal outcomes are poor, with maternal mortality up to 24% [10] and perinatal mortality 33%, related to placental abruption, intrauterine asphyxia and prematurity [13].

Aggressive treatment is indicated and delivery should be expedited, by Caesarean section if necessary [7, 8, 10], and although vaginal delivery is not contraindicated [10], fetal thrombocytopenia, present in up to 20% of cases, may make this hazardous [11].

The decrease in platelets is secondary to an increase in consumption, as bone marrow studies revealed an increase in megakaryocytes [11]. Fibrin deposition in the hepatic sinusoids may be the cause of the liver function abnormalities and the right upper quadrant pain that is often present [7]. Platelet decreases do not reach their nadir until the post-partum period in 50% of patients [12], but by day 6 post-partum the vast majority have platelet counts exceeding 100 x 10⁹ litre⁻¹ [9, 14]. Platelet transfusions are indicated if the count is less than 20 x 10⁹ litre⁻¹ for vaginal delivery and less than 50 x 10⁹ litre⁻¹ before Caesarean section [10].

Haemolytic anaemia is of the microangiopathic type. Red blood cells are damaged and altered by passing through small vessels with damaged epithelium, leading to a peripheral blood film showing burr cells and schistocytes. This follows a time course similar to that of the platelet count and liver function tests [7, 8, 11].

Laboratory diagnosis of disseminated intravascular coagulation (DIC) may be difficult. There are no definitive tests. Schistocytes are present in about 50% of cases [15] and thrombocytopenia is an early and consistent sign. PT, APTT and thrombin time are prolonged in most patients [16]. Antithrombin III concentrations are the most sensitive, with decreased concentrations in up to 97% of DIC cases [15] and this, combined with thrombin–antithrombin complexes and protein C activity was used by De Boer and colleagues [17] to reveal a higher level of compensated DIC than would have been apparent on routine coagulation tests (APTT, PT, INR) and screens for DIC (fibrinogen, platelets, FDP) in HELLP patients compared with non-HELLP patients with pre-eclampsia.

Using a scoring system introduced by Hellgren, Egberg and Eklund [18], Van Dam and colleagues [19] also found a high incidence of DIC in HELLP patients, with the extent of dysfunction maximal on day 1 post-partum. Using the simpler criteria of decreased platelets, low fibrinogen and FDP > 40 mg litre⁻¹, Sibai and colleagues [13] found DIC present in 38% of patients with this syndrome. FDP are non-specific unless greater than 40 mg litre⁻¹ but 15% of patients with DIC have concentrations < 40 mg litre⁻¹. FDP also have a long half-life of 5–72 h and so do not always reflect current coagulation status [15].

Hasegawa [20] investigated 553 cases of presumptive intravascular coagulation by fibrinogen, fibrinopeptide A, antithrombin III, plasminogen, FDP and alpha₂-plasmin inhibitor and the TEG. Of the laboratory tests only FDP and fibrinogen concentrations were thought to have rapid and simple diagnostic value, while the others were too time consuming.

The dose of heparin used during haemodialysis was small (approximately 500 u. h⁻¹ over 5–6 h) but heparin is a specific activator of antithrombin III and therefore inhibits several proteolytic enzymes, including factors IXa, Xa and thrombin. Antithrombin III neutralizes free thrombin rapidly and retards or stops its further formation. Heparin may be released from the antithrombin III–enzyme complex and become available for other molecules of antithrombin III and so small amounts can lead to inactivation of large amounts of enzyme, perhaps...
Thrombelastography and HELLP syndrome

providing a possible reason for the effect of a small dose of heparin. Heparin can also influence the antithrombin III action on Xlla, Xla, Xa, plasmin and thrombin [21].

Thrombelastography has been available for many years [22]. Its use has been described in cardiac surgery [23] in which it could have helped to avoid excessive treatment of coagulation abnormalities, and also in liver surgery [24], where it aided early management of hypercoagulable states and reduced progression to DIC by avoiding consumption of clotting factors.

In the non-operative setting, the TEG has been shown to be a more sensitive measure of heparin activity than APPTT [25] and its use allowed reduction of heparin dose for antithrombotic therapy in 66% of patients. It has also been used to construct normal ranges of measurements for normal parturients and for those with varying degrees of pre-eclampsia, including the HELLP syndrome. Chadwick and colleagues [26] found that there was a significant reduction in the alpha angle in those with severe pre-eclampsia and the HELLP syndrome compared with normal, and a significant reduction in maximum amplitude and A60 in HELLP patients compared with normal labouring women. This suggests an underlying hypocoagulable state in those with severe pre-eclampsia and HELLP syndrome. Patients with mild pre-eclampsia had hypercoagulable TEG.

In laboratory studies Egeblad and Astrup [4] showed the effect of plasmin fibrinolysis on the TEG as a reduction in amplitude but at high concentrations the lysis may be so rapid that the amplitude is barely visible. The same type of trace, with normal progression to maximum amplitude, and afterwards decreasing to zero, can be produced with activators of fibrinolysis such as streptokinase.

Zuckerman and colleagues [27] compared the TEG with common coagulation tests (PT, APTT, packed cell volume, platelet count, fibrinogen and FDP) in a group of 141 normal volunteers and 121 patients with various malignancies which they called the “hypercoagulable” group. The TEG variables correctly classified 96.7% of the hypercoagulable group compared with 72.3% by the standard tests, that is there was a higher false negative rate in this group. They concluded that this was because laboratory tests are performed on isolated fractions of blood whereas the TEG uses whole blood and therefore analyses the interactions of all blood components from the initiation of clot formation to clot lysis and retraction.

In this case report the normal coagulation profile for the day on which we began TEG monitoring (PT 15 s, APTT = 35 s, INR = 1.2, albeit after a 3-litre plasma exchange and 14 u. of FFP) was at odds with the abnormal TEG, which was a flat trace consistent with gross disturbance of coagulation, interference by anticoagulants, or both, and with the clinical picture of a patient with spontaneous haemorrhage from i.v. access sites and the vagina. Overcoming the effect of heparin in vitro using celite in the TEG sample revealed the contribution from the small dose of anticoagulant and for specific treatment in the form of protamine to be given. After administration of protamine the trace was characteristic of fibrinolysis and this also was treated specifically with aprotinin.

References