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Thrombelastography changes in pre-eclampsia and eclampsia

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Summary

We have measured platelet count, bleeding time and thrombelastography (TEG) variables and the correlation between these variables in 49 pregnant patients presenting with pre-eclampsia or eclampsia. Eighteen patients (37 %) had a platelet count $\leqslant 150 \times 10^9$ litre^{-1} and seven (14 %) had a platelet count $\leqslant 100 \times 10^9$ litre^{-1}. Bleeding time was prolonged >9.5 min in 13 (27 %) patients and the TEG was abnormal in four (8 %). The TEG variables, *k* time and maximum amplitude (MA) had a strong correlation with platelet count (*k* time–platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = -0.68$, $P = 0.003$, platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = -0.84$, $P = 0.02$; MA – platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = 0.72$, $P = 0.001$, platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = 0.78$, $P = 0.04$). There was no correlation between bleeding time and thrombocytopenia (platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = -0.18$, ns; platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = 0.09$, ns). There was no correlation between bleeding time and any measured TEG variable. Of the 10 (20 %) patients with an adequate platelet count ($> 100 \times 10^9$ litre^{-1}) but prolonged bleeding time, the TEG was normal, suggesting adequate haemostasis. An MA of 53 mm, which is the lower limit for normal pregnancy, correlated with a platelet count of 54×10^9 litre^{-1} (95 % confidence limits 40–75 $\times 10^9$ litre^{-1}). Although the number of patients with severe thrombocytopenia was small, a platelet count of 75×10^9 litre^{-1} should be associated with adequate haemostasis. (*Br. J. Anaesth*. 1996; **77**: 157–161)

Key words

Blood, coagulation. Measurement techniques, thrombelastography. Anaesthetic techniques, regional. Complications, pre-eclampsia.

Normal pregnancy is associated with an increased incidence of thrombocytopenia, with 6.6 % of pregnant women presenting with platelet counts less than 150×10^9 litre^{-1} [1]. In addition, pre-eclampsia may complicate up to 12 % of pregnancies and is often associated with abnormalities of haemostasis [2]. Although thrombocytopenia may occur in up to 50 % of patients with severe disease [3], clotting factors are rarely affected [4]. Platelet dysfunction may also be present as tests of platelet aggregation [5] and bleeding times may be abnormal [6], despite adequate platelet numbers. Parturients also frequently require extradural anaesthesia and despite the ready availability of platelet counts and coagulation tests, the lower limit of platelet count at which safe regional anaesthesia can be performed is unclear. In addition, the relevance of platelet dysfunction and the usefulness of the bleeding time are uncertain. Thus there is a need for a specific, sensitive and rapid bedside test of haemostasis [7].

The thrombelastograph (TEG) is an on-site monitor that measures all phases of coagulation to clot retraction [8]. Its usefulness, compared with standard laboratory tests of coagulation, has been described during liver transplantation [9] and after cardiopulmonary bypass [10]. TEG changes in normal pregnancy and labour [11–13], and in pre-eclampsia [14, 15] have been reported.

The aim of this study was first, to assess if the TEG could be used to detect haemostatic abnormalities in patients with pre-eclampsia or eclampsia, as demonstrated by abnormal platelet counts and standard laboratory tests of coagulation; second, to determine if a correlation existed between any TEG variable and platelet count to determine a platelet count at which TEG variables become abnormal, thus enabling some guidelines for a lower limit of platelet count at which regional anaesthesia should be avoided; and third, to use the TEG to assess overall haemostasis in a group of patients with normal platelet counts but prolonged bleeding times.

Patients and methods

Approval for the study was obtained from the Professional and Ethics Standards Sub-Committee of the Faculty of Medicine, University of Natal. Informed consent was obtained from all patients, except those with eclampsia. Patients presenting to the delivery suite with a diagnosis of pre-eclampsia

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or eclampsia were entered into the study. Mild pre-eclampsia was defined as a systolic pressure > 140 mm Hg, diastolic >90 mm Hg and proteinuria >0.3 g litre^{-1} (1 or 2+ using dipstick measurement). Severe pre-eclampsia was diagnosed by one or more of the following criteria: systolic pressure > 160 mm Hg, diastolic pressure >110 mm Hg or proteinuria >5 g litre^{-1} (3 or 4+). The diagnosis of eclampsia was based on a documented history of a recent convulsion in any patient presenting with other features of pre-eclampsia without any previous history of epilepsy and in whom no other cause for convulsions could be determined. Patients with a history of bleeding disorders or recent ingestion of antiplatelet medication within the previous week were excluded.

After admission, arterial pressure was recorded and i.v. infusion of crystalloid started. Blood was sampled through a 19-gauge steel Butterfly needle using a three-syringe technique. The first sample was discarded, the second used for laboratory tests and the third sample used for TEG measurement. This last sample was obtained in a polypropylene syringe and transferred immediately to a polypropylene tube from which 0.36 ml of whole blood was pipetted into the prewarmed cuvette of a thrombelastograph (Thrombelastograph D, Helige, Freiburg in Breisgau). The TEG was situated in the delivery suite facilitating rapid commencement of measurement and was performed in a standard manner.

Bleeding time was measured using a modified Ivy technique with a disposable Simplate II (Organon, Durham) device on the lateral aspect of the volar surface of the forearm. Before incision a sphygmomanometer cuff was inflated to 40 mm Hg and blotting paper was used every 30 s to remove the blood without touching the edges of the incision. All bleeding time tests were performed by the same person (C.E.P.O.) and the TEG result was not available until completion of the bleeding time.

The following laboratory tests were obtained: haematology (haemoglobin, platelet count and mean platelet volume (mpv)), biochemistry (urea, creatinine, calcium, magnesium, albumin and uric acid), coagulation tests (prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and clotting factors (fibrinogen, antithrombin III, protein C, factors V and VIII, and fibrin degradation products). Platelet counts were measured by automatic Coulter Counter.

Patients were studied as soon as possible after admission to the obstetric unit and choice of prophylaxis against or pharmacological control of convulsions and management of hypertension was the decision of the attending obstetrician.

Data were analysed using Pearson's correlation coefficients. Spearman's correlation was used if the groups were small ($n < 10$). Non-linear regression models were fitted to describe relationships between variables where appropriate. Patients were also evaluated further according to their platelet count: $\leqslant 150 \times 10^9$ litre^{-1} or $\leqslant 100 \times 10^9$ litre^{-1}. Values are expressed as mean (SD) and $P < 0.05$ was considered significant.

Results

We studied 49 patients over a 3-month period. The study group comprised seven patients with mild pre-eclampsia, 33 with severe pre-eclampsia and nine with eclampsia. Of the 49 patients, 18 (37 %) had a platelet count $\leqslant 150 \times 10^9$ litre^{-1} and seven of these (14 % of total) $\leqslant 100 \times 10^9$ litre^{-1}. Tests of coagulation (prolonged PT and reduced fibrinogen) were outside the normal range in two patients. In both of these patients, platelet count was less than 100×10^9 litre^{-1} and the TEG was abnormal. The TEG was abnormal in another two patients (total 8 %), with MA reduced in all four. Three of these patients presented with the lowest platelet counts in the series (30, 36 and 59 $\times 10^9$ litre^{-1}). The fourth patient had a platelet count of 286×10^9 litre^{-1}, normal PT, APTT and fibrinogen, normal bleeding time but mpv was 7.4 fl (normal range 7.4–10.4 fl). The patient with a platelet count of 30×10^9 litre^{-1} and reduced MA (43 mm) also had prolonged r (10.5 min) and k (6.0 min) times but normal PT, APTT and fibrinogen. In addition to the reduced MA, k time (5.5 min) was prolonged in another patient with a prolonged PT (13 s). Laboratory data, TEG variables and bleeding times are shown in table 1 and the number of patients with abnormal results according to platelet count are shown in table 2.

Table 1 Haematology and clothing results, TEG variables and bleeding times for all pre-eclamptic and eclamptic patients, and normal pregnancy values. Results are mean (SD). No significant differences between the two groups

Variable	Normal pregnancy	Term pre-eclampsia–eclampsia
Haematology		
Haemoglobin (g dl^{-1})	> 10	10.9 (1.5)
Platelet count ($\times 10^9$ litre^{-1})	> 150	199 (90)
Mean platelet volume (fl)	7.4–10.4	9.7 (1.5)
Coagulation tests		
PT (s)	10.2 (0.6)	10.4 (0.9)
APTT (s)	28.5 (3.1)	24.9 (3.6)
Fibrinogen (g dl^{-1})	5.3 (1.0)	5.4 (1.4)
Fibrin degradation products (ng ml^{-1})	< 200	327 (682)
Factor V (%)	109 (15)	105 (36)
Factor VIII (%)	204 (46)	245 (129)
ATIII (%)	98 (10)	83 (15)
Protein C (%)	85 (12)	89 (29)
Template bleeding time		
Bleeding time (min)	2.5–9.5	8.5 (4.7)
TEG		
r time (min)	7.8 (0.9)	6.8 (1.0)
k time (min)	3.3 (0.7)	3.1 (0.8)
MA (mm)	59.7 (3.5)	61.7 (6.6)

Table 2 Number of patients according to platelet count ($\times 10^9$ litre^{-1}) with corresponding abnormalities in TEG and bleeding time (BT). *This patient did not have an abnormal bleeding time

	No.	MA < 53 mm	BT < 9.5 min
Platelets < 50	2	2	1
Platelets 50–100	5	1	2
Platelets 100–150	11	0	5
Platelets > 150	31	1*	5

Table 3 Correlation coefficients (*P* value) between platelet count (PC), fibrinogen, fibrin degradation products (XDP) and TEG variables (*k* time and MA).

	k (min)	MA (mm)
Platelet count		
All patients ($n = 49$)	−0.37 (0.009)	0.35 (0.01)
PC $\leqslant 150 \times 10^9$ litre ($n = 18$)	−0.68 (0.003)	0.72 (0.001)
PC $\leqslant 100 \times 10^9$ litre^{-1} ($n = 7$)	−0.84 (0.02)	0.78 (0.04)
Fibrinogen		
All patients ($n = 49$)	−0.35 (0.02)	0.50 (0.0003)
PC $\leqslant 150 \times 10^9$ litre^{-1} ($n = 18$)	−0.60 (0.01)	0.72 (0.001)
PC $\leqslant 100 \times 10^9$ litre^{-1} ($n = 7$)	−0.69 (0.08)	0.86 (0.01)
XDP		
All patients ($n = 49$)	0.54 (0.0001)	−0.52 (0.0001)
PC $\leqslant 150 \times 10^9$ litre^{-1} ($n = 18$)	0.57 (0.02)	−0.67 (0.003)

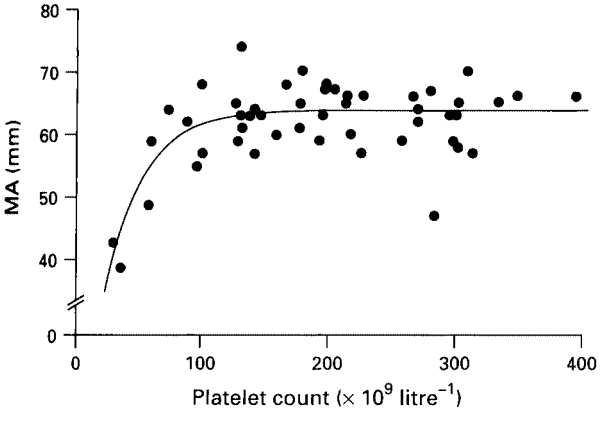

Figure 1 Scattergram of maximum amplitude (MA) of the thrombelastograph *vs* platelet count. The equation MA = $63.9 \times (1 - \exp(-0.033 \text{ platelets}))$ represents a negative exponential curve of best fit which has been calculated using a non-linear regression procedure.

Drug therapy (number of cases) at the time of evaluation included methyldopa (30), dihydralazine (22), nifedipine (8), diazepam (7), phenobarbitone (22), magnesium (10) and dexamethasone (8).

Correlation coefficients between platelet counts, fibrinogen and fibrin degradation products, and TEG variables, *k* time and MA, are shown in table 3; none of the above correlated with *r* time. There was no significant correlation between any TEG variable and PT, APTT, TT, factors V and VIII, antithrombin III, protein C, and serum concentration of urea, creatinine, calcium, magnesium and albumin.

There was a strong correlation between the TEG variables, *k* time and MA, and platelet count (*k* time–platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = -0.68$, $P = 0.003$, platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = -0.84$, $P = 0.02$; MA–platelet count $\leqslant 150 \times 10^9$ litre^{-1}, $r = 0.72$, $P = 0.001$, platelet count $\leqslant 100 \times 10^9$ litre^{-1}, $r = 0.78$, $P = 0.04$). Figure 1 shows a "hockey stick" relationship between MA and platelet count for all 49 patients. However, this relationship was linear for those seven patients with a platelet count $\leqslant 100 \times 10^9$ litre^{-1}. An MA of 53 mm, which is our lower limit for normal pregnancy (table 1), correlated with a platelet count of 54×10^9 litre^{-1} (95 % confidence limits 40–75 $\times 10^9$ litre^{-1}) (fig. 1). For all patients, there was a weak but significant negative correlation between bleeding time and platelet count ($r = -0.41$, $P = 0.003$), but no significant correlation in those patients with a platelet count $\leqslant 150 \times 10^9$ litre^{-1} or those with a platelet count $\leqslant 100 \times 10^9$ litre^{-1} ($r = -0.18$ and 0.09 respectively) (fig. 2). Bleeding time was prolonged in 13 (27 %) patients. In those with a platelet count $> 100 \times 10^9$ litre^{-1}, 10 (20 %) patients had prolonged bleeding times despite a normal TEG. There was no correlation between bleeding time and any TEG variable (*r* time = −0.18, *k* time = 0.24, MA = −0.26).

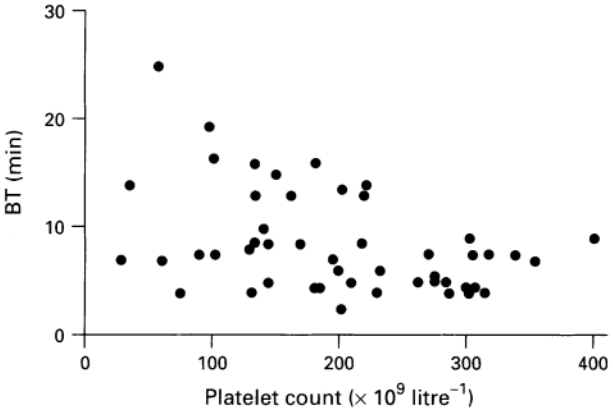

Figure 2 Scattergram of bleeding time (BT) *vs* platelet count. There was only a weak ($r = 0.41$, $P = 0.003$) correlation between the two variables.

Discussion

Platelet counts less than 150×10^9 litre^{-1} have been reported in 6.6 % and less than 100×10^9 litre^{-1} in 1.2 % of pregnant women in a study of more than 15 000 deliveries [1]. The major causes were incidental thrombocytopenia of pregnancy (74 %) and hypertensive diseases of pregnancy (21 %). Severity of pre-eclampsia is an important determinant of the effect on platelets, with thrombocytopenia in up to 50 % with severe disease [3]. Because coagulation factors are rarely reduced and only in the presence of thrombocytopenia, platelet count is a good screening test, with tests of coagulation reserved for those with reduced platelets [4]. These tests are generally available in most hospitals, but in practice time taken for these results to be available can vary enormously. However, the lower limit of platelet count at which regional anaesthesia can be performed safely is not clear, the importance of platelet dysfunction in pre-eclampsia is uncertain and the clinical relevance of bleeding time has been questioned [16]. Thus a machine that assesses haemostasis easily and rapidly in the delivery suite might not only be useful as a screening device but also may provide further information on overall clot formation in patients with reduced platelet counts or those at risk from platelet dysfunction.

The TEG is useful as it is compact, easily located within the delivery suite, relatively easy to use and produces initial results within 30 min.

The TEG measures whole blood clotting and the interaction between the protein coagulation cascade, fibrinogen and the platelet surface, from initiation of clotting to the final stages of clot lysis or retraction [8]. Thus the TEG has been found to be particularly useful during liver transplantation [9] and after cardiopulmonary bypass [10].

In normal pregnancy, reports of changes in the TEG are similar to normal values and are consistent with the hypercoagulable changes in pregnancy [12]. TEG changes of hypocoagulability have been described in a group of patients with severe pre-eclampsia, reduced platelet count and increased aspartate aminotransferase (AST) concentrations [14]. The TEG was used to diagnose and subsequently treat two episodes of haemorrhage in a patient with HELLP syndrome where conventional tests of coagulation were unhelpful [17]. Its use in three non-obstetric patients, with potential haemostatic abnormalities before regional anaesthesia, has also been described [18]. The TEG was used to assist risk of bleeding in a patient with idiopathic thrombocytopenic purpura with a reduced platelet count who underwent uneventful extradural anaesthesia [19].

In our small series, the TEG performed satisfactorily as a screening test compared with platelet count and laboratory tests of coagulation (PT, APTT and fibrinogen). MA was reduced in four patients. Three of these had the lowest platelet counts of the series. In the fourth patient, although platelet count appeared adequate, mean platelet volume (mpv) was 7.4 fl (normal pregnancy 7.4–10.4 fl). As mpv is increased in patients with pre-eclampsia [20], mpv was low for this patient. Platelet aggregation to ADP, collagen or adrenaline is directly proportional to platelet volume [21] and in thrombocytopenic patients, reduced mpv has been shown to be associated with an increased incidence of bleeding episodes [22]. As the TEG has been shown to correlate with platelet aggregation after cardiopulmonary bypass [23], the reduced MA is best explained by platelet dysfunction associated with smaller platelets.

Abnormalities of coagulation were rare in our study and in keeping with the findings of others that prolongation of the PT and APTT is seen only in those in whom platelet count is less than 100×10^9 litre^{-1} [4]. In our series, PT was slightly prolonged in two patients and associated with an abnormal TEG. TEG variables reflect the interdependence of platelets and clotting factors because the TEG is determined in whole blood, unlike laboratory tests which measure isolated aspects of coagulation in plasma. This is clearly illustrated in one patient with a platelet count of 30×10^9 litre^{-1} and reduced MA. Both *r* and *k* times were prolonged but PT and APTT were normal. Platelet phospholipid is necessary for the activation of factor X and prothrombin, and in the presence of a very low platelet count, the clotting cascade is affected, resulting in prolonged *r* and *k* times. In contrast, as phospholipid substitute is added during laboratory measurements, PT and APTT were normal. Our findings of a correlation between fibrin degradation products and MA and *k* are consistent with the documented inhibitory effects of fibrin degradation products on the conversion of fibrinogen to fibrin [24].

The 37 % incidence of thrombocytopenia (platelet count $<150 \times 10^9$ litre^{-1}) in our patients with severe pre-eclampsia/eclampsia is similar to other studies: 34 % in a group of patients with severe disease [25] and 20 % in a group with both mild and severe disease [6]. Unfortunately, there are no clear guidelines in the literature on the safe level of platelet count at which extradural anaesthesia can be performed safely. In this study, none of the patients with a platelet count less than 100×10^9 litre^{-1}, a prolonged bleeding time or an abnormal TEG received a regional anaesthetic.

Anaesthetists are reluctant to perform an extradural block in patients with platelet counts less than 100×10^9 litre^{-1} [26], although a limit of 80×10^9 litre^{-1} has been suggested [27]. Our overall finding of a low correlation between TEG variables and platelet count has been reported previously in pregnant [12] and non-pregnant subjects [28]. This finding is not surprising as the TEG, by measuring overall clot strength, would be expected to remain relatively constant over a wide normal range of platelets. However, it is only when platelet numbers start to decrease to below a critical level that any linear relationship between TEG variables (*k* and MA) and platelet count is seen. Although the number of patients with a platelet count $<100 \times 10^9$ litre^{-1} in our series was small, we have calculated that a platelet count of 54×10^9 litre^{-1} is associated with adequate TEG derived clot formation (95 % confidence limits 40–75 $\times 10^9$ litre^{-1}). As the upper limit of our 95 % confidence interval for this relationship is a platelet count of 75×10^9 litre^{-1}, we conclude that patients with pre-eclampsia with platelet counts greater than this should not have regional anaesthesia denied to them. In another series of patients with severe pre-eclampsia, TEG was normal in three patients with a platelet count of 50–100 $\times 10^9$ litre^{-1} [14]. Thus there is increasing evidence that regional anaesthesia is not contraindicated in patients with platelet counts as low as 75×10^9 litre^{-1}. At this time and because we do not have sufficient data, we cannot recommend that the TEG be used in isolation from an automated platelet count in deciding whether or not to use regional anaesthesia in a patient with severe pre-eclampsia. However, this is unlikely to happen because of the ready availability of automated platelet count machines. As more units obtain TEG machines we shall be able to assess more adequately the value of the TEG in conjunction with platelet count.

Bleeding time has been described to test for adequacy of haemostasis in those with reduced platelets [27, 29]. We found this test particularly unhelpful. One patient with a platelet count of 30×10^9 litre^{-1}, reduced fibrinogen, prolonged PT and abnormal TEG had a bleeding time of only 4 min. We were unable to demonstrate any correlation between platelets and bleeding time in those with a platelet count $<100 \times 10^9$ litre^{-1}, in contrast with a study by Ramanathan and colleagues who reported a correlation of -0.76 in this group [6].

Platelet function is altered in pre-eclampsia and *in vitro* platelet aggregation may be reduced despite the presence of a normal platelet count [5]. Bleeding time has been used to test for this platelet defect and has been found to be prolonged in 34 % of patients with severe pre-eclampsia and a platelet count $> 100 \times 10^9$ litre^{-1} [6] and in 25 % with a platelet count $> 150 \times 10^9$ litre^{-1} [25]. In our patients with severe pre-eclampsia, 20 % had a prolonged bleeding time in the presence of a platelet count $> 100 \times 10^9$ litre^{-1}, yet the TEG was normal. The TEG is sensitive to qualitative abnormalities of platelets and a significant positive correlation between MA and platelet aggregation and collagen and adenosine diphosphate after cardiopulmonary bypass has been demonstrated [23]. Based on our findings, excluding these patients for regional anaesthesia is inappropriate.

Because *in vivo*, clotting occurs on cell surfaces rather than in plasma, the TEG performed on whole blood may provide a better indicator of the dynamics of clot formation than standard laboratory tests of coagulation which are measured in plasma. However, *in vivo*, haemostasis begins with platelet adhesion to the damaged vessel wall, and the TEG cannot measure this initial interaction between platelets and vascular endothelium. As a result, if the platelet defect is caused by interference with the normal interaction between platelets and vascular endothelium, then the TEG is unable to detect this effect, as occurs in uraemic patients or patients receiving aspirin [30]. Pre-eclampsia is associated with endothelial damage, impaired production of prostacycline and increased deposition of fibrin within the vascular bed. The TEG does not measure these local changes, but can be used to determine the effects on overall clotting associated with reduced platelet counts.

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