Obstetrical and Pediatric Anesthesia

Platelet count may predict abnormal bleeding time among pregnant women with hypertension and preeclampsia

[La numération plaquettaire peut permettre de prédire le temps de saignement chez des parturientes atteintes d'hypertension et de pré-éclampsie]

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Background: Anesthesiologists often require laboratory data to estimate the bleeding risk among hypertensive pregnant women prior to administering regional anesthesia. Many rely on the bleeding time (BT) in making this determination. We examined whether the platelet count can adequately predict BT among a group of hypertensive parturients.

Methods: This retrospective subgroup analysis, taken from a cohort of 2051 hypertensive pregnant women, comprises 87 individuals who underwent both a BT and platelet count prior to delivery. We calculated the correlation between the platelet count and BT at three platelet cut-off points with respect to prolonged BT of eight minutes or more.

Results: There was a significant negative correlation between platelet count at delivery and BT [$r = -0.45$, 95% confidence interval (CI) -0.26 to -0.60 ; $P < 0.0001$]. All three platelet cut-off points had a sensitivity of less than 66% with negative predictive values below 75% for an abnormal BT. A platelet count $\leq 75 \times 10^9/L$ was specific for the presence of an abnormal BT (specificity 97.8%, 95% CI 91.7–100.0), with a positive predictive value of 95.5% (95% CI 83.1–100.0) and a positive likelihood ratio of 24 (95% CI 3.3–168).

Conclusions: In a group of hypertensive parturients, the platelet count appears to be very specific for predicting a prolonged BT. The

platelet count may aid the anesthesiologist in determining the risk of bleeding from regional anesthesia. Given the study's potential for bias future research is needed to validate these findings.

Objectif : Avant d'administrer une anesthésie régionale, les anesthésiologistes exigent souvent des examens de laboratoire pour évaluer le risque de saignement chez les femmes enceintes. Beaucoup se fient au temps de saignement (TS) pour ce faire. Nous avons vérifié si la numération plaquettaire (NP) permet de prédire adéquatement le TS chez des parturientes hypertendues.

Méthode : L'analyse rétrospective a porté sur un sous-groupe de 87 personnes choisies à partir d'une cohorte de 2 051 femmes enceintes hypertendues qui ont subi un TS et une NP avant l'accouchement. Nous avons calculé la corrélation entre la NP et le TS selon trois niveaux seuils du décompte plaquettaire en regard d'un TS prolongé de huit minutes ou plus.

Résultats : Il y a eu une corrélation négative significative entre la numération plaquettaire à l'accouchement et le temps de saignement [$r = -0.45$, intervalle de confiance (IC) de 95 % -0.26 à -0.60 ; $P < 0.0001$]. Les trois niveaux seuils plaquettaires ont présenté une sensibilité de moins de 66 % et des valeurs prédictives négatives de

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Source of funding: A grant-in-aid was provided by the Department of Obstetrics and Gynecology, and the Division of Nephrology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Accepted for publication December 4, 2000.

Revision accepted February 5, 2001.

moins de 75 % pour un TS anormal. Un décompte plaquettaire $\leq 75 \times 10^9/L$ était caractéristique de la présence d'un TS anormal (spécificité de 97,8 %, IC de 95 % 91,7–100,0), avec une valeur prédictive de 95,5 % (IC de 95 % 83,1–100,0) et un rapport des vraisemblances positif de 24 (IC de 95 % 3,3–168).

Conclusion : La numération plaquettaire s'est révélée très spécifique d'une prédiction de TS prolongé chez un groupe de parturientes hypertendues. Cet examen peut aider l'anesthésiologiste à déterminer le risque de saignement résultant de l'anesthésie régionale. Étant donné la présence possible de biais dans notre étude, il faudra chercher à valider ces résultats.

BOTH thrombocytopenia and acquired coagulopathies may arise in up to 20% of women with preeclampsia and gestational hypertension.^{1–5} These patients often require rapid Cesarean delivery, leaving the anesthesiologist with the dilemma of providing optimal analgesia while minimizing bleeding risk.^{6,7} This decision may be further complicated by the unpredictability of hemorrhagic misadventure, such as epidural hematoma with the use of neuraxial anesthesia,^{8,9} and the perceived potential for litigation.¹⁰ Although many obstetrical anesthesiologists now use the platelet count, international normalized ratio (INR) and activated partial thromboplastin time (aPTT) as indicators of hemorrhagic risk,^{11,12} others continue to rely on the bleeding time (BT) in certain situations.^{13,14}

Since its introduction nearly a century ago arguments have been made for^{15,16} and against^{17–19} the use of the BT to predict hemorrhagic risk, including that associated with regional anesthesia.¹⁸ The association between the platelet count and BT has also been debated. For example, a hallmark study by Harker and Slichter found a strong correlation between platelet count and BT,²⁰ a finding corroborated by a study of women with preeclampsia.²¹ However, other reports contradict these findings.^{3,17} A recent statement by the College of American Pathologists and the American Society of Clinical Pathologists concluded that the BT cannot accurately predict the risk of surgical hemorrhage, and that a normal BT does not exclude the possibility of excessive hemorrhage during an invasive procedure.¹¹ This statement also addressed the use of the BT in situations where bleeding risk cannot be evaluated by history alone.¹¹ Thus, there remains ongoing controversy about the best way to determine bleeding tendency among individuals at higher than average risk, such as a pregnant woman with preeclampsia and non-proteinuric gestational hypertension.

Recent evidence suggests that the platelet count is a practical and cost-effective means for excluding the presence of a coagulopathy in women with toxemia.²² In addition, previous survey data have identified a heavy reliance on the platelet count in the evaluation of bleeding risk in the preeclamptic population.²³ Accordingly, we examined the association between BT and platelet count in a cohort of pregnant women with hypertension during pregnancy. Our primary goal was to determine the test properties of the platelet count in predicting an abnormal BT among parturients with both proteinuric and non-proteinuric forms of hypertension during pregnancy. We further discuss the practical limitations of both the BT and platelet count in assessing bleeding risk in the particular context of neuraxial anesthesia.

Methods

We conducted a retrospective subgroup analysis derived from a large prospective cohort study, called *MOS HIP* (McMaster Outcome Study of Hypertension in Pregnancy). The current study hypothesis and data analysis were developed and conducted following the completion of data collection for *MOS HIP*. Between January 1986 and December 1995, all pregnant women with a sitting systolic blood pressure 140 mmHg or diastolic pressure >90 mmHg were prospectively entered into *MOS HIP*. Preeclampsia and gestational hypertension were classified according to the taxonomy and definitions of the 1990 National High Blood Pressure Education Program Working Group.²⁴ Preeclampsia was defined by the presence of hypertension in association with 2+ proteinuria on urinary dipstick or at least 300 mg of urinary protein per 24-hr specimen collection.²⁴

Participants were consecutively recruited into *MOS HIP* at the time of delivery and accounted for 98% of all women with hypertension who delivered at our hospital during this period. Data were collected from the mother's hospital chart by two authors (R.B. and E.B.) within three months after delivery, abstracted to a standard data collection form and subsequently entered into a database (SPSS, SPSS Inc, Chicago, IL). Prior to delivery, a complete blood count, including automated platelet count, was conducted in all women. If the platelet count was below normal (i.e., $150 \times 10^9/L$), a manual count was performed. In addition, prothrombin time (PT), aPTT, and fibrinogen level were assessed.

The subgroup of women in *MOS HIP* who underwent BT evaluation was included in the current analysis. BTs were completed by a hematology technician using a surgicutt BT device according to the method of

Mielke.^{25,26} The timing and indications for the BT were not typically documented in the patient's chart and the test was done at the discretion of the attending physician. We did not collect data on the type of anesthesia or analgesia provided at delivery, or complications related to neuraxial anesthesia or maternal hemorrhage.

Baseline maternal and neonatal characteristics, among those who had a BT done, were compared with those who did not; similar comparisons were made among those whose BT was normal (i.e., less than eight minutes) *vs* abnormal (i.e., greater than or equal to eight minutes); (Table I). Baseline characteristics were compared using one-way ANOVA for continuous variables and a chi-square test for categorical data. All *P* values were two-sided, and a significance level of 0.05 was chosen. Statistical analyses were performed using SAS Version 6.12 (SAS Institute Inc., Cary, North Carolina, USA).

In an unmasked fashion, we calculated the Pearson correlation coefficient between the platelet count and BT at delivery, with a 95% confidence interval (CI). A partial correlation coefficient, controlling for the PT and aPTT, was also calculated. Because experimental controlled studies have shown that aspirin,^{17,27,28} but not magnesium sulphate,^{29,30} may prolong the BT, we re-calculated both the Pearson and partial correlation

coefficients after excluding women who had received aspirin within one week prior to delivery.

We also evaluated BT (i.e., below *vs* above eight minutes) with respect to three different platelet count cut-off points (i.e., $50 \times 10^9/L$, $75 \times 10^9/L$, and $100 \times 10^9/L$). The use of the cut-off point of eight minutes to define an abnormal BT was based on data from other studies,³¹ textbooks,³² and the upper limit of normal of our own centre. Data were entered into a 2 x 3 table, and the sensitivity and specificity, positive (PPV) and negative predictive (NPV) values, as well as positive and negative likelihood ratios (LR) were calculated, together with their respective 95% CI. These test properties were then re-calculated after excluding women who had received aspirin within one week of delivery.

The McMaster University Medical Ethics Committee was consulted at the commencement of the study in 1986. They decided that formal consent was not required because all maternal and newborn personal identifiers were omitted upon database entry, which preserved patient anonymity and prevented future patient contact.

Results

Participant characteristics

During the study period, 2051 women with hypertension were included, 87 of which (4.2%) had a BT done

TABLE I Characteristics of 2051 consecutive pregnant women with hypertension or toxemia who either did or did not undergo a bleeding time (BT) evaluation before delivery

Characteristic or outcome	BT ≥ 8 min	BT < 8 min	No BT done	Statistical test*
Total no. (%) women	41 (2.0)	46 (2.2)	1964 (95.8)	—
Mean (SD) maternal age	28.0 (4.1)	29.0 (5.4)	29.4 (5.1)	<i>P</i> =0.2
Mean (SD) gravidity	1.6 (0.8)	2.4 (2.0)	2.1 (1.4)	<i>P</i> =0.03
Mean (SD) parity	0.4 (0.7)	0.6 (1.0)	0.6 (0.9)	<i>P</i> =0.4
No. (%) singletons	38 (92.7)	41 (89.1)	1869 (95.2)	<i>P</i> =0.1
No. (%) chronic hypertension	1 (2.4)	5 (10.9)	467 (23.8)	<i>P</i> <0.001
No. (%) preeclampsia or the HELLP syndrome	38 (92.7)	33 (71.7)	631 (32.1)	<i>P</i> <0.001
No. (%) gestational hypertension	2 (4.9)	8 (17.3)	866 (44.1)	<i>P</i> <0.001
No. (%) received aspirin	2 (4.9)	5 (10.9)	34 (1.7)	<i>P</i> <0.001
No. (%) received magnesium sulfate	10 (24.4)	7 (15.2)	48 (2.2)	<i>P</i> <0.001
No. (%) Cesarean delivery	29 (70.7)	28 (60.9)	877 (44.6)	<i>P</i> <0.001
Mean (SD) gestational age at delivery, weeks	32.8 (4.3)	34.1 (3.8)	36.5 (3.7)	<i>P</i> <0.001
No. (%) delivery <37 weeks	33 (80.5)	32 (69.6)	742 (37.8)	<i>P</i> <0.001
No. (%) delivery <32 weeks	14 (34.1)	12 (26.1)	233 (11.9)	<i>P</i> <0.001
Mean (SD) neonatal birthweight, g	1761.6 (879.8)	2076.8 (972.7)	2725.4 (1000.0)	<i>P</i> <0.001
Mean (SD) platelet count at delivery, $\times 10^9/L$	88 (49)	200 (145)	227 (77)	<i>P</i> <0.001
No. (%) women with platelet count $\leq 75 \times 10^9/L$ at delivery	21 (51.2)	1 (2.2)	54 (2.7)	<i>P</i> <0.001
Mean (SD) PT, seconds	12.3 (1.1)	12.0 (0.5)	12.0 (0.5)	<i>P</i> <0.001
Mean (SD) aPTT, seconds	32.6 (6.8)	29.7 (3.9)	30.0 (4.5)	<i>P</i> <0.001
Mean (SD) fibrinogen level, g/L	4.9 (1.2)	5.1 (1.1)	5.2 (1.5)	<i>P</i> = 0.4

* Group means were compared using a one-way ANOVA, while rates were compared using a chi-square test.

PT Prothrombin time (normal: 11 to 13 sec); aPTT Activated partial thromboplastin time (normal: 24 to 37 sec).

TABLE II Test properties of three different platelet count cut-off points compared to an abnormal bleeding time (BT) of eight minutes or greater among pregnant women with hypertension or preeclampsia

Platelet count cut-off point ($\times 10^9/L$)	Test characteristic	Abnormal BT ≥ 8 min
≤ 50 vs $> 50^*$	Sensitivity (%; 95% CI)	32.0 (18.5–46.5)
	Specificity (%; 95% CI)	97.9 (91.9–100.0)
	PPV (%; 95% CI)	92.9 (74.2–100.0)
	NPV (%; 95% CI)	62.1 (50.1–72.8)
	+LR	14.9 (2.0–109.0)
	-LR	0.7 (0.6–0.9)
≤ 75 vs > 75	Sensitivity (%; 95% CI)	51.2 (36.1–66.2)
	Specificity (%; 95% CI)	97.8 (91.7–100.0)
	PPV (%; 95% CI)	95.5 (83.1–100.0)
	NPV (%; 95% CI)	69.2 (57.6–79.8)
	+LR	23.6 (3.3–168.0)
	-LR	0.5 (0.4–0.7)
≤ 100 vs > 100	Sensitivity (%; 95% CI)	65.9 (50.8–79.4)
	Specificity (%; 95% CI)	80.4 (67.9–90.5)
	PPV (%; 95% CI)	75.0 (61.0–89.0)
	NPV (%; 95% CI)	72.5 (59.6–83.8)
	+LR	3.4 (0.3–0.7)
	-LR	0.4 (0.3–0.7)

*A value of "1" was substituted for a 0-value cell for the calculation of the test properties of a platelet count below $50 \times 10^9/L$.

PPV=Positive predictive value; NPV=Negative predictive value; +LR= Positive likelihood ratio; -LR=Negative likelihood ratio.

prior to delivery (Table I). The rate of eclampsia varied from approximately 0.1% in the gestational hypertension group to 3.9% among those with preeclampsia. None received anticoagulants prior to delivery and less than 5% of all participants received magnesium sulphate prophylaxis. The characteristics of all MOS HIP participants are outlined in Table I. Of the 87 women studied, 41 (47.1%) had a prolonged BT. There were several significant differences between groups, including the observation that women with a prolonged BT were more likely to have a diagnosis of preeclampsia or HELLP syndrome (92.7%) compared to those whose BT was normal (71.7%) or who did not undergo a BT (32.1%).

Hematological profile

The hematological profile of study participants is shown in Table I. The mean platelet count at delivery was significantly lower among those with a prolonged BT ($88 \times 10^9/L$) than those with a normal BT ($200 \times 10^9/L$). A platelet count $75 \times 10^9/L$ at delivery was observed among 76 of 2051 study participants (3.7%), and was more prevalent among women with an abnormal BT (51.2%) than those with a normal BT (2.2%)

FIGURE Platelet count vs bleeding time.

or those in whom a BT was not done (2.7%). The mean PT and aPTT were slightly higher in the group with a prolonged BT, but all mean values were within normal limits for our hospital laboratory.

Correlational analyses

A significant negative correlation between platelet count at delivery and BT ($r = -0.45$, 95% CI -0.26 to -0.60 ; $P < 0.0001$) was observed (Figure). The magnitude of the relationship was greater after excluding women receiving aspirin ($r = -0.58$, 95% CI -0.41 to -0.71 ; $P < 0.0001$). The partial correlation coefficients, controlling for PT and aPTT, were similar: -0.42 ($P < 0.0001$) among all 87 women and -0.57 ($P < 0.0001$) among those not receiving aspirin.

Test properties

Table II presents the test properties of the different platelet count cut-off points in relation to the BT. Among women with a platelet count below $50 \times 10^9/L$, none had a normal BT; accordingly, a value of "1" was assigned to this group in order to estimate the test properties at that platelet count cut-off point. All three platelet cut-off point values had a low sensitivity for the detection of an abnormal BT, varying from as low as 32% for a platelet count $50 \times 10^9/L$, to nearly 66% for a count $100 \times 10^9/L$. The corresponding NPVs were all below 75% (Table II).

A platelet count $75 \times 10^9/L$ was specific for the presence of a BT over eight minutes (specificity 97.8%, 95% CI 91.7–100.0), with a PPV of 95.5% (95% CI 83.1–100.0) and a positive LR of 24 (95% CI 3.3–168); (Table II). The test properties for a platelet count $50 \times 10^9/L$ were largely the same as those for a count $75 \times 10^9/L$. A platelet count cut-off point of $100 \times 10^9/L$ had a somewhat lower specificity (80.4%, 95% CI 67.9–90.5), PPV (75.0%, 95% CI 61.0–89.0) and

positive LR (3.4, 95% CI 1.8–6.3). After excluding seven women who were taking aspirin, the test properties of the various platelet cut-off points remained essentially unchanged (data available upon request).

Discussion

Among a large prospective cohort of women with various forms of hypertension in pregnancy, we found that fewer than 5% either underwent a BT analysis or developed a thrombocytopenia below $75 \times 10^9/L$ prior to delivery. In a retrospective subgroup analysis of women within this cohort who underwent a BT, a platelet count below $75 \times 10^9/L$ appeared to be moderately insensitive, but very specific, for identifying those with a prolonged BT.

The decision to also include pregnant women with non-proteinuric forms of hypertension (i.e., chronic and gestational hypertension)²⁴ was made because we did not know why these women had a BT ordered, and thus, could not be certain that they were no more hypertensive or ill than women with overt proteinuria (i.e., preeclampsia). Similarly, the finding of non-proteinuric hypertension and thrombocytopenia in a parturient may have represented a variant of preeclampsia in advance of the manifestation of overt proteinuria, which often develops only at a later stage.²⁴

There are several potential sources of bias within our study that require comment.

First, this was a *post hoc* subgroup analysis from a larger cohort study and, accordingly, we did not collect data on or control for certain relevant factors, such as the indication for the BT. Similarly, those who ordered a BT were not masked to the patient's platelet count or severity of toxemia; the higher rate of thrombocytopenia and preeclampsia among the women who underwent a BT supports this point. Finally, we did not assess whether the BT was measured prior to or during the first stage of labour; a condition of heightened anxiety which may slightly augment the BT.¹⁷ Accordingly, we must interpret our findings with caution, particularly the apparently high specificity and PPV of the platelet count for a prolonged BT.

The absence of a normotensive pregnant control group presents another limitation to our study, especially given the paucity of literature surrounding BT variations during uncomplicated pregnancy.^{2,17} Thus, our definition of an abnormal BT (i.e., greater or equal to eight minutes) may have been inappropriately applied, leading to another source of bias in our estimation of the platelet count-BT test properties. Finally, in the absence of data on hemorrhagic events in this population, we cannot draw inferences about the predictive value of the platelet count for this outcome.

Notwithstanding the above limitations, these findings do add to a scarce body of literature on the utility of the platelet count in estimating, but not defining, the risk for hemorrhage among women with hypertension in pregnancy before delivery. The CIs around the estimates were quite narrow, and, assuming that the high specificity and PPV test properties of a low platelet count are only somewhat biased, it is likely that these data can be of some practical use to clinicians.²¹

It has been demonstrated that a prolonged BT predicts a decline in the hematocrit value, and could be indirect evidence of excess hemorrhage.^{33,34} However, this concept has been countered by the observation that anemia itself, in the face of a normal platelet count, can prolong the BT.¹⁷ Furthermore, it is known that the BT may be prolonged due to a variety of conditions that are independent of platelet quantity or function.¹⁷

We have observed that a platelet count of $75 \times 10^9/L$ or less may be quite specific for the presence of an abnormal BT. When a woman's platelet count is below this value, it is unlikely that a BT measurement can add much to the estimation of bleeding risk, since our data suggest that the BT will likely be prolonged. However, a platelet count of $100 \times 10^9/L$ or greater is less specific (80%), while remaining insensitive (66%), for a prolonged BT. At this point, the clinician may require another method to estimate the probability that a bleeding diathesis is present, as well as to evaluate the risk for a major hemorrhagic event.

Although the risk of traumatic neuraxial hemorrhage remains a major issue for the obstetrical anesthesiologist,^{8,9} there are few established risk factors for this serious but rare event.^{8,9,35} The development of a spinal hematoma is not guaranteed in the face of a prolonged BT and would likely remain a rare event even in the presence of a bleeding diathesis. Increasing experience and the use of more modern techniques for neuraxial blockade, including the selective use of a single spinal block instead of insertion of an epidural catheter, could translate into a lower baseline risk for traumatic hemorrhage. Although our data may aid in clinical decision-making, we encourage further discussion and the development of more precise estimates of bleeding risk in this population.

A large prospective cohort study might optimally determine which risk factors and hematological markers are important predictors of bleeding risk among both normotensive and hypertensive pregnant women. By comparing these women to those with gestational thrombocytopenia,³⁶ one may shed further light on bleeding abnormalities peculiar to women with preeclampsia. Finally, although spinal hematomas

are extremely rare, neuraxial anesthesia is used frequently enough that a large international registry could provide a valuable mechanism to identify risk factors for spinal hematoma.

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