

Coagulation screening tests in high risk neonates: a prospective cohort study

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Abstract

Forty seven infants in a prospective cohort of 170 high risk neonates without signs of overt bleeding had abnormal coagulation screening tests within 36 hours of birth. Early thrombocytopenia was a better predictor of prolonged prothrombin times and hypofibrinogenaemia than very low birth weight, fetal growth retardation, or poor five minute Apgar scores.

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Although the occurrence of neonatal thrombocytopenia has been studied,¹ little is known about the prevalence of plasma clotting defects in unselected high risk infants. We therefore performed coagulation screening tests within 36 hours of birth in a prospective cohort of critically ill neonates. We also examined whether abnormalities of plasma coagulation can be predicted by early low platelet counts and several other generally accepted risk factors such as very low birth weight, fetal growth retardation, and low five minute Apgar scores.

Subjects and methods

SUBJECTS

The study was conducted in the neonatal intensive care unit at McMaster University between April 1989 and March 1990. All infants admitted to the unit were eligible for enrolment if the following two criteria were met: (i) postnatal age less than 36 hours and (ii) indwelling arterial catheter with undampened pressure tracing. The latter ensured recruitment of the group of patients in the nursery who were most ill and also allowed artifact free blood sampling. The study was approved by the Institutional Review Board for research involving human subjects.

The decision to place an arterial catheter for monitoring purposes was made by the attending medical staff without reference to this study. Patency of the catheter was maintained with an infusion of 5% dextrose containing 1 U/ml heparin at a rate of 1 ml/hour. All flushing solutions were heparin free. Apart from the administration of 24 U/day heparin, no study patient received anticoagulant or thrombolytic drugs. Vitamin K (0.5-1.0 mg) was given parenterally at birth to all infants. Administration of blood products during the six hours preceding the study sample was recorded in all subjects.

COAGULATION ASSAYS

Blood samples (0.9 ml) for coagulation

studies were drawn once from the free flowing arterial catheter at the time of medically ordered sampling for complete blood counts. The prothrombin time was determined using human thromboplastin (Thromborel S, Behringwerke, Germany), and expressed as the international normalised ratio (INR)

$$\text{INR} = \left(\frac{\text{Patient prothrombin time}}{\text{Control prothrombin time}} \right)^{\text{ISI}}$$

where ISI is the international sensitivity index of the thromboplastin used in the local laboratory.² Fibrinogen was measured using the method of Clauss.³ Platelet counts $<150 \times 10^9/l$, fibrinogen concentrations $<1.5 \text{ g/l}$, and an INR >1.5 were considered abnormal in all study patients.^{1,4} Plasma samples were shown to be free of heparin contamination by protamine titration.

ANALYSIS

Observed frequencies and 95% confidence intervals of laboratory abnormalities were determined. Sensitivities, specificities, predictive values, and likelihood ratios were calculated to assess whether birth weight $<1500 \text{ g}$, gestational age <29 weeks, five minute Apgar scores <6 , and platelet counts $<150 \times 10^9/l$ predicted abnormalities of plasma coagulation.⁵ As fetal growth retardation has been implicated as a risk factor of coagulopathy, the frequency of plasma coagulation defects was also examined in infants with birth weights below the tenth centile according to local population based standards.⁶

Results

STUDY INFANTS

During the 12 month study period, 191 infants fulfilled the two entry criteria, 177 of whom were entered into the study. Fourteen infants were either missed, or sampled after the first 36 hours of life. Seven blood samples were mislabelled or clotted. For ethical reasons the study protocol did not allow repeat samples to be drawn in these instances. Thus results are reported for 170 infants, or 89% of all potentially eligible infants. Table 1 summarises the

Table 1 Characteristics of the 170 infants studied

Gestational age (weeks)	29 (24-41)*
Birth weight (g)	1380 (600-5300)*
Sex (male/female)	93/77
In/outborn	123/47
5 minute Apgar score	7 (2-10)*
Postnatal age (hours)	16.6 (0.8-35.5)*
No with mechanical ventilation at time of study	144
No with fresh frozen plasma infusions before study	27

*Values are median (minimum-, maximum) values.

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important characteristics of the study group. No infant had received blood products for clinical bleeding before the coagulation screen. Twenty seven infants were given up to 20 ml/kg of fresh frozen plasma to improve hypovolaemia and hypotension during the six hours preceding the blood sample. Coagulation screening tests were entirely normal in 67% of patients who received plasma, compared with 63% of those who did not. Owing to the considerable overlap of the respective 95% confidence intervals (46.0 to 83.5% *v* 54.5 to 70.9%), the effect of the plasma infusions on the test results was not considered important enough to justify stratification of subsequent analyses according to plasma use.

ABNORMALITIES OF COAGULATION SCREENING TESTS

Table 2 gives the observed frequencies of abnormal tests together with the 95% confidence intervals. Of the 47 infants with abnormal plasma coagulation, 18 patients had an increased INR, whereas 16 subjects had a low fibrinogen concentration. In a further 13 infants the two tests were abnormal. Among infants with an abnormal INR, the median value was 1.7 (maximum 3.1). Among infants with hypofibrinogenaemia the median fibrinogen concentration was 1.1 g/l (minimum 0.3 g/l). The median platelet count in the 36 infants with thrombocytopenia was $118 \times 10^9/l$ (minimum $36 \times 10^9/l$).

PREDICTION OF COAGULOPATHY

Table 3 summarises the sensitivities, specificities, predictive values, and likelihood ratios for all examined risk factors of coagulopathy.

Discussion

Abnormalities of the coagulation system are reported to be common in ill neonates, yet little is known about the prevalence of plasma clotting defects in unselected high risk infants. In this prospective cohort study coagulation

screening tests were abnormal within the first 36 hours in about one third of all infants who were sick enough to require an indwelling arterial catheter for monitoring purposes. Abnormalities of plasma coagulation could not be predicted accurately by more readily known risk factors such as immaturity, fetal growth retardation, or poor Apgar scores. The strongest predictor of coagulopathy was thrombocytopenia. Infants with platelet counts $<150 \times 10^9/l$ were 3.7 times more likely to have plasma coagulation defects than infants with normal platelet counts. Further, normal INR and fibrinogen values were less than half as likely to be found in infants weighing <1500 g than in larger infants. Low birth weight, however, was not a strong predictor of abnormal plasma coagulation. Thus our data suggest that screening for coagulopathy will have the highest yield in infants with early thrombocytopenia whereas infants with birth weights >1500 g are least likely to have laboratory evidence of coagulopathy.

The clinical significance of abnormal coagulation screening tests is currently uncertain. Although no infant was noted to bleed overtly at the time of the study, occult haemorrhage may well have contributed to the morbidity of these critically ill infants. This hypothesis is supported by previous descriptions of an association between abnormal coagulation tests and the presence and severity of intracranial haemorrhage in preterm infants.⁷⁻¹⁰ Trials of fresh frozen plasma or other preparations of coagulation factors in the prevention of intracranial haemorrhage have yielded conflicting results.¹¹ Further studies are therefore required to determine whether sick newborn infants would benefit from the detection and correction of clinically inapparent clotting defects.

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Table 2 Abnormalities of coagulation screening tests in 170 high risk neonates

Coagulation profile	No (%) of occurrences	95% Confidence interval (%)
Normal	108 (64)	55.8 to 70.8
Coagulopathy	26 (15)	10.2 to 21.6
Coagulopathy and thrombocytopenia	21 (12)	7.8 to 18.3
Thrombocytopenia	15 (9)	5.0 to 14.1

Table 3 Prediction of coagulopathy

Predictor	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Likelihood ratio
Birth weight:					
<1500 g (n=97)	77		37		
≥1500 g (n=73)		50		85	0.46
Gestational age:					
<29 weeks (n=64)	51		38		1.6
≥29 weeks (n=106)		67		78	0.73
Small for gestational age:					
Yes (n=20)	17		40		
No (n=150)		90		74	0.92
Apgar score					
<6 (n=26)	22		38		1.6
≥6 (n=141)*		87		74	0.90
Platelet count:					
< $150 \times 10^9/l$ (n=36)	45		58		3.7
≥ $150 \times 10^9/l$ (n=134)		88		81	0.63

*Three missing values in infants not born in this hospital.

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