Early Human Development (2005) **81**, 35–41

ELSEVIER

Early Human Development

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Neonatal thrombocytopenia

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KEYWORDS
Neonatal thrombocytopenia;
Platelets;
Platelet transfusion;
Alloimmune thrombocytopenia

Abstract Thrombocytopenia occurs in up to a third of preterm neonates admitted to intensive care units. In these babies, thrombocytopenia typically presents in one of two patterns: early-onset thrombocytopenia occurring within 72 h of birth and late-onset thrombocytopenia which develops after 72 h. Early-onset thrombocytopenia is most commonly caused by disorders associated with placental insufficiency (e.g. maternal hypertension), is mild-moderate, self-limiting and requires no treatment; it is caused by reduced platelet production. Late-onset thrombocytopenia is usually due to bacterial sepsis or necrotising enterocolitis; it is often severe (platelets $<50\times10^9$/l), prolonged and requires treatment with platelet transfusions. In term babies, neonatal thrombocytopenia is usually severe and most commonly caused by bacterial sepsis, perinatal asphyxia or neonatal alloimmune thrombocytopenia. There is a lack of evidence-based guidelines for treatment of neonatal thrombocytopenia. The most important future developments will depend upon studies aimed at determining optimal platelet transfusion schedules for term and preterm neonates.

1. Introduction

With the exception of phlebotomy-induced anaemia, thrombocytopenia is the commonest haematological abnormality encountered in the neonatal period [1]. Although there is a vast number of causes of neonatal thrombocytopenia, including rare inherited causes [1–3], only a few are commonly encountered in neonatal practice and are therefore most clinically relevant. The spectrum of thrombocytopenia includes, on the one hand, the extremely sick premature neonate with profound thrombocytopenia secondary to sepsis in whom the impact of a major haemorrhage may be catastrophic but whose survival will depend mainly on successful treatment of infection, and, on the other hand, severe isolated thrombocytopenia in a term neonate who is otherwise well and for whom the clinical outcome may solely depend on the impact of the thrombocytopenia. It is therefore

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doi:10.1016/j.earlhumdev.2004.10.013

important to recognise the common causes of thrombocytopenia and identify appropriate investigation and management of individual cases.

Our understanding of the pathogenesis and natural history of neonatal thrombocytopenia has improved considerably in recent years. This helps us provide appropriately tailored management in individual cases and paves the way for new therapeutic approaches. In this review, we will discuss our current knowledge of the incidence, pathogenesis and management of neonatal thrombocytopenia.

2. Definition of thrombocytopenia

By the end of the first trimester of pregnancy, the fetal platelet count has already reached 150×10^9/l [4] and rises further to $175–250\times10^9$/l by the middle of the second trimester [5]. Thus, platelet counts of $<150\times10^9$/l define thrombocytopenia in any neonate regardless of gestational age. Although the healthy fetus or neonate can generate and maintain a circulating platelet count similar to that of adults, several studies indicate that sick neonates often have reduced platelet producing capacity compared to that of adults and this may become increasingly evident during times of increased platelet demand [1,6,7].

3. Incidence of neonatal thrombocytopenia

The incidence of neonatal thrombocytopenia varies greatly, depending upon the population studied, from <1% in healthy term babies to around one third of neonates admitted to neonatal intensive care units (NICU). In a recent, population-based prospective study in Helsinki of 4489 term infants, they found that the incidence of thrombocytopenia (platelet counts of $<150\times10^9$/l) on cord blood testing was 2% (95% CI 1.5–2.3) with severe thrombocytopenia (platelet counts $<50\times10^9$/l) occurring in 0.24% of cases (95% CI 0.10–0.38) [8]. In another large study of 8388 newborns, thrombocytopenia ($<150\times10^9$/l) was found in 0.5% of cases (95% CI 0.3–0.6), of which 0.12% were severe (platelet count $<50\times10^9$/l) (95% CI 0.05–0.20) [9]. However, the incidence of thrombocytopenia in preterm neonates in NICU is much higher, consistently reaching 22–35% in our unit, with severe thrombocytopenia (platelets $<50\times10^9$/l) in 6% of all admissions (these babies) [8,9]. Data from other recent studies are more difficult to interpret since they include only neonates with platelet counts $<100\times10^9$/l or, because of methodological difficulties, have under-represented neonates of low birth weight, the high risk population for neonatal thrombocytopenia [10].

4. Causes of neonatal thrombocytopenia

4.1. Natural history of thrombocytopenia as a guide to diagnosis

Recent studies show that most cases of neonatal thrombocytopenia fall into two main groups depending upon the age of the neonate when the

Table 1 Causes of fetal and early neonatal thrombocytopenia

Placental insufficiency
Maternal hypertension
Intrauterine growth restriction (IUGR)
Maternal diabetes
Immune
Alloimmune
Autoimmune (maternal ITP)
Neonatal lupus
Infection
Congenital: *CMV*, *toxoplasma*, rubella, HIV, coxsackie
Perinatal: *Group B streptococcus*, *Haemophilus influenzae*, *E. coli*
Congenital/inherited
Aneuploidy: *trisomies 13, 18 and 21*; triploidy
Bone marrow failure affecting megakaryocytes (e.g. congenital amegakaryocytic thrombocytopenia, thrombocytopenia absent radii syndrome)
Bone marrow failure syndromes with pancytopenia (e.g. Fanconi anaemia)
Myelodysplasia (e.g. Monosomy 7)
Immunodeficiencies (e.g. Wiskott Aldrich, Haemophagocytic Lymphohistiocytosis)
Platelet function disorders with thrombocytopenia (e.g. Bernard Soulier syndrome)
Disseminated intravascular coagulation
Perinatal asphyxia
Bacterial infection
Whole body cooling
Congenital thrombotic thrombocytopenic purpura (ADAMTS-13 deficiency)
Other (rare in most NICU)
Thrombosis-aortic, renal
Kasabach Merritt
Hepatic haemangioendothelioma
Metabolic-propionic acidaemia, methylmalonic acidaemia
Congenital leukaemia
Heparin-induced thrombocytopenia (HIT)
Subcutaneous fat necrosis of the newborn (SCFN)
Exchange transfusion
Rhesus haemolytic disease of the newborn

Commonest causes shown in italics.