The Relation between Etiology and Outcome of Neonatal Thrombocytopenia in Neonatal Intensive Care Unit of Zagazig University Hospital

Thesis

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The Etiology and Prognosis of Neonatal Thrombocytopenia in Neonatal Intensive Care Unit of Zagazig University Hospital

ABSTRACT

Background: In busy NICUs evaluation and management of patients with neonatal thrombocytopenia is an everyday occurrence. In most cases, simple clinical and laboratory evaluation provides the cause of the thrombocytopenia and allows a prediction of its clinical course. Thrombocytopenia defined as platelet count of < $150x10^9$ /L in any neonate regardless of gestational age. The incidence of neonatal thrombocytopenia varies greatly from <1.1 in healthy term babies to around one third of neonates admitted to NICU. The incidence of Thrombocytopenia in preterm neonates in NICU is in much higher, reaching 22.35%, with severe thrombocytopenia (platelets <50 $x10^9$ /L) in 6% of all admission. Thrombocytopenia in the newborn rarely is indicative of a primary disorder of megakaryopoiesis, but more often is the result of either systemic illness or transfer of maternal antibodies directed against fetal platelets.

Objective: Our study aimed to estimate the causes, severity and outcome of neonatal thrombocytopenia in neonates admitted to our NICU.

Methods: his study was carried out on 172 neonates with thrombocytopenia admitted to Neonatal Intensive Care Unit of Zagazig university hospital during the period from the 1st of July 2013 till the end of June 2014. The inclusion criteria were all neonates (Term and preterm), While the exclusion criteria were severe congenital malformation.

Results: Our results revealed that: There was a significant difference between the studied groups regarding weight and non significant difference between the studied groups regarding gestational age and postnatal age. Sepsis was the most common associated clinical condition in the studied groups. The most frequent associated maternal diseases were pregnancy induced hypertension and diabetes mellitus. The most common sites of major hemorrhage was pulmonary hemorrhage (5.8%) followed by GIT hemorrhage (5.2%) and intraventricular hemorrhage (4.7%). There was a significant difference between the studied groups regarding platelet, whole blood, Extremely low birth weight (ELBW) and NEC were associated with higher incidence of moderate and severe thrombocytopenia. Bleeding was found to be related to severity of thrombocytopenia and to lesser extent to late onset thrombocytopenia. There was improvement in most cases due to proper treatment. Mortality in thrombocytopenic neonates was higher in preterm neonates. Bleeding, moderate or severe thrombocytopenia and early onset thrombocytopenia were associated with increased mortality.

Conclusion: Neonatal thrombocytopenia is an existing problem in our neonatal intensive care units (NICUs) related to many etiological factors. Sepsis are the most common causes of late onset thrombocytopenia whereas placental insufficiency and perinatal asphyxia are related to early onset thrombocytopenia. The most common causes of neonatal thrombocytopenia were bacterial sepsis, pregnancy-induced hypertension, asphyxia and disseminated intravascular coagulation.

Keywords: Neonatal thrombocytopenia, Neonatal sepsis, Immune thrombocytopenia

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List of Abbreviations

Abb.	Term

ADP ..... : *Adenosine Diphosphate*

ATRUS ……..: *Amegakaryocytic thrombocytopenia with radioulnar synostosis*

CMV ..... : *Cytomegalovirus*

CVS ..... : *Chorionic Villous Sampling*

DB ..... : *Dense Body*

DIC ..... : *Disseminated Intravascular Coagulation*

DMS ..... : *Demarcation Membrane System*

ECMO ..... : *Extracorporeal Membrane Oxygenation*

ELBW ..... : *Extremely Low-Birth Weight*

FBS ..... : *Fetal Blood Sampling*

FMAIT ..... : *Fetomaternal Alloimmune Thrombocytopenia*

GP ..... : *Glycoprotin*

HGFs ..... : *Haemopoietic Growth Factors*

HIV ……: *Human immune deficiency virus*

HPA ..... : *Human Platelet Antigen*

ICH ..... : *Intra Cranial Haemorrhage*

IPF ……..: *Immature platelet fraction*

ITP ..... : *Immune Thrombocytopenia*

IUGR ..... : *Intra Uterine Growth Retardation*

IVH ..... : *Intraventricular Haemorrhage*

IVIgG ..... : *Intravenous Immunoglobulin G*

LAMP ..... : *Lysosomal Associated Membrane Protine*

MAIPA ..... : *Monoclonal Antibody Immobilization of Platelet Antigen*

MPV ..... : *Mean Plattelet*

NAIT ……: *Neonatal alloimmune thrombocytopenia*

NEC ..... : *Necrotizing Enterocolitis*

NICU ..... : *Neonatal Intensive Care Unit*

List of Abbreviations (Cont...)

Abb.	Term

PAF ..... : *Platelet Activating Factor*
PA-IgG ..... : *Platelet Associated Immunoglobulin G*
PCR-SSP ..... : *Chain Reaction-Sequence Specific Primers*
PDGF ..... : *Plattelet Derived Growth Factor*
PF4 ..... : *Plattelet Factor 4*
PIH ..... : *Pregnancy-Induced Hypertension*
PLC ..... : *Phospholipase C*
PP ..... : *Pseudopodium*
PUBS ..... : *Percutaneous Umbilical Blood Sampling*
rhTpo ..... : *Recombinant human Tpo*
RP ..... : *Reticulated Platelet*
rTpo ..... : *Recombinant Thrombopoietin*
SCCS ..... : *Surface Connected Canalicular System*
SGA.....: *Small for gestational age*
SLE ..... : *Systemic Lupus Erythematosis*
TAR ..... : *Thrombocytopenia-Absent Radius*
TPO ..... : *Thrombopoietin*
TpoR ..... : *Tpo Receptor*
TXA2 ..... : *Thromboxane A2*
VEGF ..... : *Vascular Endothelial Growth Factor*
VLBW ..... : *Very Low-Birth Weight*
VWF ..... : *Von Willbrand Factor*

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INTRODUCTION

Thrombocytopenia is a commonly encountered hematologic problem among sick neonates affecting up to 35% of infants admitted to the Neonatal Intensive Care Unit (NICU). Although multiple conditions have been casually associated with neonatal thrombocytopenia, the cause of the thrombocytopenia is unclear in up to 60% of the affected neonates ***(Schrezenmeier and Seifried, 2010)***.

Platelets first appear in the human fetus at five weeks post-conception, and increase in number during fetal life, reaching normal adult values by 22 weeks of gestation ***(Ferrer-Marin et al., 2010).***

Neonatal thrombocytopenia is generally defined as a platelet count less than 150,000/μl. Degrees of thrombocytopenia can be further subdivided into mild (platelet count 100,000 to 150,000/μl), moderate (platelet count 50,000 to 99,000/μl) and severe (platelet count <50,000/μl) ***(Gunnink et al., 2014).***

By the end of the first trimester of pregnancy, fetal platelet count has already reached 150 x 10^9/L and rises further to 175-250 x 10^9/L by the middle of second trimester. Thus, platelet counts of < 150 x 10^9/L define thrombocytopenia in any neonate regardless of gestational age. The significance of platelet counts between 100,000 and 150,000/μl in neonates is

unclear, however, because a higher of counts in this range is found in otherwise healthy neonates. Thrombocytopenic infants mostly have evidence of the underlying impaired fetal megakaryocytopoiesis and platelet production following pregnancy complications characterized by placental insufficiency or fetal hypoxia. However, many neonatal complications exacerbate these thrombocytopenic potentials and 20% of thrombocytopenics in NICU patients are severe ***(Tynngard, 2009).***

About75% of NICU cases are considered mild or moderate, and do not warrant intervention. Among extremely low birth weight infants, a high proportion is classified as severe. Severe neonatal thrombocytopenia is associated with significant morbidity, although correlation between platelet count and incidence of bleeding is poor. The evaluation and the management of the neonate with thrombocytopenia is a challenge. Therefore, a review of classification, pathogenesis, practical approach, and management of neonatal thrombocytopenia is important ***(Carciolo , 2016).***

In approximately 75% of all neonates with thrombocytopenia, the thrombocytopenia is transient and/or mild, and does not require prompt intervention. However, one or more platelet transfusions are ordered in an attempt to treat or decrease the risk of hemorrhage. In the case of neonates with active major hemorrhage (intracranial, pulmonary, GI, hepatic, renal), most experts agree that platelet transfusions should be

administered for platelet counts $<100\times10^9$/L. However, the great majority of transfusions are administered to non bleeding neonates, and there is significant variability in neonatal transfusion practices among institutions and among individual neonatologists ***(Chaudhary and Clarke, 2008).***

Causes of neonatal thrombocytopenia can usually be determined by the clinical history and presentation ***(Chakravorty et al., 2012).*** Thrombocytopenia which presents after the first 3 days of life is due to sepsis or necrotizing enteroclitis (NEC) in >80% of cases. The most frequent cause of early-onset thrombocytopenia is associated with chronic fetal hypoxia, as occurs in infants born to mothers with pregnancy-induced hypertension or diabetes and/ or in those with intrauterine growth restriction (IUGR) ***(Roberts et al, 2008).*** Neonates suffering from infections with viral pathogens such as human immunodeficiency virus (HIV), cytomegalovirus (CMV), or enterovirus frequently exhibit thrombocytopenia with incompletely understood mechanisms ***(Sola-Visner et al., 2009).***

Aim of the Work

The aim is to study the relation between different causes, and outcome of neonatal thrombocytopenia in neonatal intensive care unit (NICU), of Zagazig University Hospital.

REVIEW OF LITERATURE

Platelet Morphology and Ultrastructure

Platelets or thrombocytes, the smallest of blood cellular elements, are the cell fragments of megakaryocytes circulating in the blood. They have a critical role in cellular mechanisms of primary hemostasis leading to the formation of blood clots. Dysfunction or low levels of platelets predisposes to bleeding, while high levels, although usually asymptomatic, may increase the risk of thrombosis ***(Slichter, 2006)***.

Several researchers have been carried out on blood platelets to study their morphology. In quiescent stage, platelets circulate as small, anucleats, biconvex, discoid cells having mean diameter of 2-4 μm and mean volume of 7-8 femotiliter. Young platelets may be 2.3 times as large; decrease in size with aging was suggested ***(Stanworth et al., 2009)***.

Platelets are known to be heterogeneous with respect to size, buoyant, functional capacity, organelle content and metabolic properties. Since newborn platelets are already highly heterogeneous in size, decrease in platelet size with aging may increase or decrease the overall platelet heterogeneity depending on whether or not it affects platelet fractions uniformly ***(Liumbruno et al., 2009)***.

In a Wright-Giemsa-stained film, platelets appear as small, bright, round or elongate bodies with a delicately