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RESEARCH ARTICLE

Thrombocytosis in the neonatal intensive care unit: Experience at a single center

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ABSTRACT

Although thrombocytosis is frequently detected in newborns, few reports have focused on its risk factors. This report documents the characteristics of 89 neonates with thrombocytosis followed up in a neonatal intensive care unit (NICU). We reviewed the patients' medical and laboratory records retrospectively to determine the associated conditions and risk factors for neonatal thrombocytosis, and complications related to thrombocytosis. We also discussed the differences of neonatal thrombocytosis from that of childhood in the light of literature. The mean platelet count of these newborns was 579.7 ± 111.5 (451-936) x 10^9/L. Associated conditions included anemia (73.7%), high-risk pregnancies (56. %), prematurity (51.7%), infections (37.1%), antenatal drug use (22.7%), indirect hyperbilirubinemia (20.2%), cardiac disorders (14.6%), respiratory distress syndrome (14.6%), history of hypoxia (13.5%), surgery (12.4%), and hemorrhage (3.4%). In most cases, more than one risk factor for thrombocytosis existed in the same newborn. No hemorrhagic complications related to thrombocytosis were observed; however, 1 newborn had portal vein thrombosis associated with intestinal malrotation. In summary, risk factors and associated conditions for thrombocytosis in newborns differed from those in children. In light of associated disorders, the mechanism of thrombocytosis in newborns may differ from that of childhood thrombocytosis.

Key Words: Etiology, neonatal intensive care unit, newborn, thrombocytosis

ÖZET

Yenidoğan yoğun bakım ünitesinde trombositoz: Tek merkezin deneyimi

Bu yenidoğanların ortalama trombosit sayıları 579.7 ± 111.5 (451-936) x 10^9/L idi. Trombositozla birlikte bulunan tıbbi durumlar şöyleydi: %73.7 anemi, %56.2 yüksek riskli gebelik, %51.7 prematürite, %37.1 infeksiyonlar, %22.7 antenatal ilaç kullanımı, %20.2 indirekt hiperbilirubinemi, %14.6 kardiyak hastaliklar, %14.6

respiratuar distres hastalıkları, %13.5 hipoksi hikayesi, %12.4 ameliyat, %3.4 hemoraji. Olguların çoğunda aynı yenidoğanda birden fazla risk faktörü bulundu. Trombositoza bağlı hemorajik bir komplikasyon görülmezken, sadece bir yenidoğanda intestinal malrotasyona bağlı portal ven trombozu mevcuttu. Sonuç olarak, yenidoğan trombositozuyla birlikte bulunan tıbbi durumlar ve risk faktörlerinin çocukluk yaş grubundan farklı olduğu bulundu.

Anahtar Sözcükler: Etyoloji, yenidoğan yoğun bakım ünitesi, yenidoğan, trombositoz

INTRODUCTION

The normal range for platelet count in children (neonates included) is 150 x 10^9/L to 450 x 10^9/L [1]. Thrombocytosis is relatively common in children younger than three years of age, and is especially frequent in the first year of life [2]. It is rare for children to have primary thrombocytosis, or to develop thrombocytosis as a result of myeloproliferative disorders. Reports indicate that thrombocytosis in children frequently occurs secondary to infection, hematological or respiratory disorders, tissue damage, surgery, and connective tissue disorders [2-8]. This condition usually features a benign course with no complications [2-8].

Although thrombocytosis is far more common in newborns than in older children [2], few reports have focused on the etiology of neonatal thrombocytosis. In this retrospective study, we documented characteristics of neonates with thrombocytosis who were hospitalized in a neonatal intensive care unit (NICU).

MATERIALS and METHODS

A total of 89 neonates with thrombocytosis (platelet count > 450 x 10^9/L) were included in the study. We first compiled a list of neonates hospitalized in the NICU who had platelet count > 450 x 10^9/L using the program Avicenna (Ankara, Turkey). A list of 108 newborns was generated, but 19 were excluded because of missing medical records. We reviewed patients' medical and laboratory records for complete blood count, gestational age, sex, high-risk pregnancy (eclampsia, diabetes, premature rupture of membranes, placental disorders, poor access to prenatal care, maternal age over 35 years), antenatal maternal drug use, associated disease(s) or condition(s) (such as prematurity, infection, anemia, surgery), transfusion requirements, and hospitalization time [2-8]. We also recorded findings for serum C-reactive protein (CRP) in cases where this had been measured, and noted any occurrences of thrombosis or hemorrhaging as complications of neonatal thrombocytosis. Anemia was defined as a hemoglobin and/or hematocrit value less than 2 standard deviations below the lower limit of the normal range for the newborn's age.

All complete blood counts were performed using a hemocytometer (Cell-dyne 3000, Abbott Diagnostics, IL, USA). CRP was measured in a Roche PP Modular unit (Mannheim, Germany) using standard kits.

Statistics

Data were analyzed with the Student's t test, chi-square test and Fisher's exact test (two-tailed). The Statistical Package for the Social Sciences (SPSS for Windows, version 11.0, SF, USA) was used. P values < 0.05 were considered to be statistically significant.

RESULTS

Table 1 summarizes some characteristics of the neonates. Forty-six (51.7%) of the 89 babies were premature (≤ 37 weeks gestation). Serial platelet counts had only been recorded for 27 of the patients. In these cases, thrombocytosis resolved in a mean of 10.7 ± 7.2 days (range, 4-35 days).

Risk Factors and Associated Conditions

Table 2 lists the risk factors and other conditions associated with thrombocytosis that were detected in the 89 cases. Thirty-three of the neonates had infection, and Table 3 summari-

Table 1. Some characteristics of the study group

Variable (n)	
Gestational age (wks) (89)	35.15 ± 4.363 (26-41)*
Mean age at time of thrombocytosis (days) (89)	14.4 ± 6.6 (3-31)
Sex (male/female) (89)	51/38 (42.7/57.3%)
Birth weight (g) (89)	2427.74 ± 903.516 (580-4500)
Hemoglobin (g/dL) (76)	12.4 ± 2.9 (7-18.7)
Leukocyte count (x 10^9/L) (72)	14.3 ± 7.7 (3.3-49)
Platelet count (x 10^9/L) (89)	579.7 ± 111.5 (451-936)
CRP (mg/dL) (47)	12.9 ± 18.2 (0.3-76.6)
Mean hospital stay (days) (89)	25.2 ± 27 (1-150)

n: Number of neonates with available data for the parameter.
* Data expressed as mean ± standard deviation (min-max) except for gender analysis
CRP: C-reactive protein.

Table 2. Risk factors and conditions associated with thrombocytosis in the study group+

Associated conditions (N)	n (%)
Anemia (76)	56 (73.7)
High-risk pregnancy (89)	50 (56.2)
Prematurity (89)	46 (51.7)
Infections (89)	33 (37.1)
Antenatal drug use (88)	20 (22.7)
Indirect hyperbilirubinemia (89)	18 (20.2)
Cardiac disorders (89)	13 (14.6)
Surgery (89)	13 (14.6)
Respiratory distress syndrome (89)	13 (14.6)
Hypoxia (89)	12 (13.5)
Hemorrhage (89)	3 (3.4)
Miscellaneous (89)	8 (9)

N: Number of neonates with available data. n: Number of neonates with the disorder.
+: Some subjects had more than one condition

zes the types of infection detected in these cases. Eighteen (54.5%) of the 33 neonates with infection were premature. The causative agent was isolated from blood and/or other cultures in 16 (48.5%) of the cases: *Pseudomonas aeruginosa* (3 cases), *Klebsiella spp.* (3 cases), *Staphylococcus epidermidis* (3 cases), *Enterobacter spp.* (2 cases), *Escherichia coli* (1 case), *Candida albicans* (1 case), respiratory syncytial virus (1 case), alpha-hemolytic *Streptococcus* (1 case), and diphtheroid species (1 case).

Thirteen (14.6%) of the 89 neonates had cardiac disorders. All but one of the babies in this group were mature newborns. Three of the newborns with cardiac disorders had a history of hypoxia. Only one had been delivered after a high-risk pregnancy. None of these 13 newborns was polycythemic, but nine were anemic. One had fetal supraventricular tachycardia, and the remaining 12 had structural congenital heart disease (CHD; 10 cyanotic and 2 acyanotic). Eleven of the 12 neonates with CHD underwent heart surgery. The remaining neonate (who had acyanotic CHD) was hospitalized due to pneumonia. Of the 11 patients who underwent surgery, 3 had thrombocytosis preoperatively and 7 developed this condition 4 to 17 days after the operation. In the remaining case, thrombocytosis was documented 8 days after the patient developed mediastinitis and sepsis. In the neonate who was hospitalized for pneumonia, thrombocytosis was detected 20 days after admission. Regarding other risk factors for thrombocytosis, 7 of the 12 neonates with CHD had various forms of infection.

Table 3. Type of infection in the study group

Infection type	n (%)
Sepsis	14 (42.4)
Bronchopneumonia	8 (24.2)
Necrotizing enterocolitis	3 (9.1)
Urinary tract infection	2 (6.1)
Meningitis + pneumonia	1 (3)
Meningitis + osteomyelitis	1 (3)
Omphalitis + skin infection[1]	1 (3)
Skin infection[2]	1 (3)
Upper respiratory tract infection	1 (3)
Mediastinitis[3]	1 (3)
Total	33 (100)

[1] Associated with dystrophic epidermolysis bullosa.
[2] Associated with epidermolysis bullosa and pyloric stenosis.
[3] Infection after surgery for congenital heart disease.

Eighteen (20.2%) of the 89 total neonates had indirect hyperbilirubinemia. Three in this group had Rh/rh isoimmune hemolytic anemia [1 of the 3 also had respiratory distress syndrome (RDS) and 1 also had cystic encephalomalacia], 2 had ABO-isoimmune hemolytic anemia, and 1 had pyropoikilocytosis. Seventeen of the patients with indirect hyperbili-

rubinemia received phototherapy, and 11 of them received phototherapy alone. Thrombocytosis was detected on the day of admission in 10 of these latter 11 cases. In the other neonate who received phototherapy alone, the condition was identified 10 days after this treatment. Two of the 3 neonates with Rh/rh isoimmune hemolytic anemia who received phototherapy and intravenous immune γ-globulin (IVIG) were diagnosed with thrombocytosis 10 and 16 days after therapy, respectively. The third had a high platelet count on admission. In the neonate with ABO-isoimmune hemolytic anemia, thrombocytosis was detected 7 and 11 days after IVIG and exchange transfusion, respectively. In the remaining 3 neonates (2 who received phototherapy and exchange transfusion, 1 who was untreated), thrombocytosis was detected on admission.

Three newborns were hospitalized because of hemorrhage. Hemorrhaging was related to hemophilia B in 1 patient who had intracranial bleeding alone. There were 2 peaks of thrombocytosis during hospitalization in this case: one at seven days after craniotomy and hematoma drainage (platelet count 537 x 10^9/L), and this resolved in 15 days; the other at seven days after the duraplasty (platelet count 999 x 10^9/L) that was performed three weeks after craniotomy. In the latter episode, the platelet count remained elevated for two weeks, and the patient was discharged with a count of 713 x 10^9/L. Another neonate with hemorrhage (intracranial and gastrointestinal bleeding) had been diagnosed with hypofibrinogenemia. This newborn had required cardiopulmonary resuscitation at birth. Thrombocytosis was detected nine days after hemorrhage was detected, and it resolved 15 days later. The third patient with hemorrhage had no bleeding diathesis and was hospitalized for gastrointestinal hemorrhage. Testing revealed Coombs'-positive hemolytic anemia at four days of age. This diagnosis was made at another center, and the patient had anemia and thrombocytosis when he was admitted to our hospital. As his anemia resolved, his platelet count also improved, and the latter was normal by five days after admission.

Fifty-six (62.9%) of the 89 subjects had anemia; only 28 (50%) of these newborns required transfusion. Twenty-nine (51.8%) of the neonates with anemia were of premature gestational age, and 32 (57.1%) were born after high-risk pregnancies. All the neonates with anemia had another associated condition or risk factor for thrombocytosis. Twenty (35.7%) of the anemic neonates had infection.

Twelve (13.5%) of the 89 neonates had a history of hypoxia and/or low Apgar score at birth. In this group, thrombocytosis was detected 9 to 24 days after birth (mean, 15.9 ± 5 days). Six of these 12 neonates were premature and 8 had anemia. Eight of these babies were born after high-risk pregnancies. Ten had risk factors for thrombocytosis and associated disorders. Seven had some type of infection. The 2 neonates with no risk factors or associated disorders were born after high-risk pregnancies, and both had to be resuscitated at birth.

Thirteen (14.6%) of the 89 neonates had RDS, and all were premature. Eight of the 10 with complete blood count parameters in their medical records had anemia. Eleven of these RDS babies were born after high-risk pregnancies. Five had risk factors for thrombocytosis and associated-disorders. Two had some type of infection.

Fifty (56.2%) of the 89 neonates were born after high-risk pregnancies. The mean time of thrombocytosis detection in this group was 15.3 ± 6.7 days after birth (range, 4-31 days). Thirty-two (64%) of these babies were diagnosed with thrombocytosis within two weeks of birth. The high-risk issues in these 50 pregnancies are listed in Table 4.

Eighty-eight of the 89 records contained information on antenatal drug use by the mother, and 20 (22.7%) of these noted antenatal drug use. Steroids were the most common agents used (10 cases). In 8 of the pregnancies, steroids were used in combination with other drugs.

No hemorrhagic complications related to thrombocytosis were observed in any of the 89 neonates in the study; however, 1 newborn had portal vein thrombosis associated with intestinal malrotation.

Table 4. List of high-risk pregnancies

High-risk issue	n
Eclampsia	6
Multiple gestation	6
Premature rupture of membranes	6
Placental disorders	6
Poor access to prenatal care	5
Diabetes mellitus	4
Maternal age over 35 years	3
Hypertension	3
Oligohydramnios	2
Hypothyroidism	1
Mitral valve disorder	1
Hepatitis B antigen carrier	1
Premature preterm rupture of membranes	1
Stomach cancer	1
Anhydramnios	1
Deep vein thrombosis	1
Urinary infection	1
Severe anemia	1
Total	50

n: Number of cases with high-risk issue.

Severity of Thrombocytosis

Results for the neonates with marked thrombocytosis (platelet count ≥ 700 x 10^9/L) were compared with findings for all other subjects. There were no significant differences between these groups with respect to sex distribution, gestational age, birth weight, history of hypoxia, presence of anemia at time of thrombocytosis detection, presence of risk factors or associated conditions, or antenatal drug use ($p > 0.05$ for all). However, the group with marked thrombocytosis had a significantly higher proportion of patients hospitalized for more than 14 days, and a significantly higher proportion of patients who required erythrocyte transfusions ($p = 0.017$ and 0.001, respectively). Analysis showed that the neonates hospitalized for more than 14 days had a 1.4-fold higher relative risk of showing marked thrombocytosis than those hospitalized for shorter periods [95% confidence interval (CI): 1.1-1.9].

DISCUSSION

The aim of this research was to document conditions associated with neonatal thrombocytosis in a NICU. We found that anemia was the most frequent associated disorder in our subjects. Thrombocytosis is reported to be associated with anemia in premature newborns who receive human recombinant erythropoietin, and in those who have infection [9,10]. In the 89 cases of neonatal thrombocytosis that we studied, the conditions that led to anemia included iatrogenic blood loss, isoimmune hemolytic anemia, hemorrhage and infection (data not presented). All of these conditions can stimulate bone marrow to produce more erythroid progenitors and increase production and/or release of platelets.

The majority of neonates in our study were born after high-risk pregnancies. One previous investigation revealed that stressful delivery influences circulating thrombopoietin levels in newborns. Ikeno et al. [11] demonstrated that both thrombopoietin and cortisol levels were greater in neonates delivered vaginally with or without maternal/fetal complications than in those delivered by cesarean section without complication. They suggested that fetal stress near the time of delivery affects thrombopoietin levels in cord blood, which may be mediated in part by the action of cortisol on thrombopoietin receptors. Other work has shown that preeclampsia and eclampsia cause higher levels of cord blood erythropoietin [12]. Teramo et al. detected high levels of erythropoietin in amniotic fluid from 13.5% of 156 diabetic pregnant women [13]. There is increasing evidence that erythropoietin promotes not only erythropoiesis, but also thrombopoiesis [14]. In our study, we were able to get antenatal drug use data for 88 of the 89 cases of neonatal thrombocytosis. Steroids were used in half of the 20 cases that featured antenatal drug use. Megakaryocytes have receptors for steroids, and steroids can induce thrombocytosis [15]. New studies may enlighten the effect of these drugs on neonatal thrombocytosis.

Many of the neonates we studied were premature, and these babies required longer hospital stays than most others in the study. Thrombocytosis occurs relatively often in premature neonates due to physiological factors and because they are frequently hospitalized

for problems related to immaturity or infection. In a previous study on healthy preterm babies, 38% of the subjects had thrombocytosis [16]. Matsubara et al. also detected early elevation of thrombopoietin levels (related to subsequent thrombocytosis) in preterm newborns [16].

We found that indirect hyperbilirubinemia was also associated with thrombocytosis in the neonates we studied. All 17 of our subjects with indirect hyperbilirubinemia received phototherapy, which has been shown to increase tumor necrosis factor-α (TNF-α), interleukin (IL)-2 and IL-10, and not change IL-6 and -3 levels [17]. However, in the majority of the patients who received phototherapy in our study, thrombocytosis was detected at time of admission. Thus, thrombocytosis of these neonates may not be related to phototherapy. Four of our patients were treated with IVIG combined with other modalities, and we detected some degree of rebound thrombocytosis 7-10 days after this treatment in three patients. IVIG therapy is known to reduce cytokine (IL-6, IL-8 and TNF-α) levels and inflammation, and thus may not be related to thrombocytosis [18]. Although phototherapy and IVIG are known to alter cytokine production, we do not know how indirect hyperbilirubinemia, phototherapy, or IVIG was related to neonatal thrombocytosis in our patient group [17,18].

A considerable proportion (13.5%) of the neonates in our study had CHD. Since our hospital is a tertiary *cardiac referral* center, this may have been a factor in the observed high frequency of CHD in neonates with thrombocytosis. In newborns with cyanotic CHD who had thrombocytosis on admission, increased production of bone marrow cells in response to tissue hypoxia may have led to thrombocytosis. Tissue hypoxia stimulates erythropoietin secretion [19], which in turn may cause both erythropoiesis and thrombopoiesis [14,20,21]. In addition, most of the neonates with CHD also had associated conditions such as heart surgery and infection that cause tissue injury and/or hypercytokinemia. This observation is in accordance with one previous study that noted marked thrombocytosis in three children after cardiovascular surgery [5].

Respiratory distress syndrome was another important condition associated with thrombocytosis in 10.1% of the neonates in our study. RDS was reported in two studies on childhood secondary thrombocytosis [5,6]. In the first study, RDS was present in 8 (11%) of 36 patients aged from 0 to 13 years [6]. In the other study, defining causes of thrombocytosis in 94 patients younger than 16 years, RDS was found in seven premature infants, and adult type RDS was detected in two children [5]. Nonetheless, how it is related to thrombocytosis is not known. There may be a link with the tissue hypoxia that occurs in this disorder.

The majority of neonates in our study had more than one risk factor or other disorder associated with thrombocytosis. In line with previous reports on thrombocytosis in childhood, our cases followed a benign course [2-8].

Nevertheless, some of the 89 neonates in the present study had conditions like bronchopneumonia, CHD, history of hypoxia at birth and RDS leading to tissue hypoxia that increases erythropoietin production and secretion. Considering associated disorders in our patient group, in addition to cytokines (such as IL-6), catecholamines and thrombopoietin, erythropoietin may be an important factor in neonatal thrombocytosis [2]. Previous studies have noted elevation of platelet counts in response to a rise in erythropoietin level [9,22-24]. These studies were performed in animals, premature babies and renal failure patients receiving recombinant erythropoietin, and women with iron-deficiency anemia and thrombocytosis [9,22-24]. As in newborns from stressful deliveries, elevated glucocorticoids may be another factor leading to neonatal thrombocytosis [11].

In summary, the risk factors and conditions associated with thrombocytosis in newborns differ from those in children. Unlike cases seen in childhood, it appears that multiple factors are usually involved in neonatal thrombocytosis. Infection is the main etiologic factor for thrombocytosis in childhood; however, our data suggest that various conditions peculiar to newborns (high-risk pregnancy,

prematurity, CHD, RDS) are also associated with thrombocytosis in NICU patients. Sepsis was the most frequent form of infection in the 89 neonates we studied. The number of different disorders associated with thrombocytosis in this patient group suggests that mechanisms of thrombocytosis in neonates and children may differ. Further investigations of the mechanisms of neonatal thrombocytosis are needed.

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