Platelets and sepsis in preterm neonates: Is there an organism-specific response?

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Abstract: Preterm babies stay in neonatal intensive care unit for a long time and they have lower immunity and need intensive procedures. These factors make them vulnerable to infection, so we need a rapid sensitive reliable marker for early detection of sepsis. **Aim of the work :**This work aimed to :1- Assess platelet count in preterm neonates with culture proved sepsis. 2-Study the relationship between different infectious agents (gram positive, gram negative bacteria and fungi) and thrombocytopenia. **Patients and Methods:** The study comprised 40 preterm newborns delivered in our hospital (25 newborns had low birth weight, 12 very low birth weight and 3 extreme low birth weight), 13 newborns had early onset sepsis while 27 had late onset sepsis. According to Bussei et al., (2005) our newborns divided into three groups according to their platelet count Group (I): included 13 newborns with mild thrombocytopenia (platelet count≤ 150,000/ mm3), Group (II): included 19 newborns with moderate thrombocytopenia (platelet count ≤ 100.000/ mm3) and Group (III): included 8 newborns with severe thrombocytopenia (platelet count ≤ 50,000/mm3). All newborns were subjected to full history taking, thorough clinical examination, close monitoring for sepsis (clinical sepsis score, hematological sepsis score and blood culture) and clinical and laboratory diagnosis of disseminated intravascular coagulopathy. **RESULT:** Platelet count decreased with decreasing gestational age, severe thrombocytopenia in 8 patients aged 31± 1.51 weeks. The lowest the birth weight the marked deficiency in platelet count. Low birth weight had mild thrombocytopenia, very low birth weight had moderate thrombocytopenia and extreme low birth weight had severe thrombocytopenia. Newborns with early onset sepsis had mild thrombocytopenia while those with late onset sepsis had moderate thrombocytopenia. Forty five percent of our patients had gram negative infection and 32.5% had fungal infection. Newborns with gram positive infection had normal platelet count, newborns with gram negative infection had mild thrombocytopenia and newborns with fungal and mixed infection had moderate thrombocytopenia. Both recovered newborns and those who died had moderate thrombocytopenia, but it was significant lower in those who died than in recovered. There is no significant difference between recovered and died groups except in platelet count which was more deficient in died group. The younger the gestational age, extreme low birth weight and fungal infection cause severe thrombocytopenia.**Conclusion:** Thrombocytopenia can be used as an early diagnostic marker for sepsis and a prognostic one. Candidemia and delay to appropriate therapy contribute to increased morbidity and mortality.
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1. Introduction

Neonatal sepsis (NS) is a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life **(Badrawi *et al.*, 2001).** The morbidity and mortality from NS continues to be a major problem **(Abdel-Hady and Zaki, 2003).**

Fungal infections are prevalent among very low birth weight (VLBW) infants and are associated with significant morbidity and mortality **(Kaufman, 2004).** Candida species rank second to fourth as the most frequent cause of late onset sepsis (LOS) in VLBW **(Stoll *et al*., 1996; Bendel, 2005 and Yalaz *et al*., 2006).** Neonatal candidemia, occurs in 4% to 15% of extremely low birth weight (ELBW) infants and the 30-day mortality approaches 40% **(Benjamin *et al.*, 2003).** Although bloodstream infection is the most common presentation, candida can disseminate and cause meningitis, renal, splenic or liver abscesses, endophthalmitis, osteomyelitis or invasive dermatitis **(Saiman *et al.*, 2000 and Rex *et al.*, 2000).**

Thrombocytopenia occurs, in up to one third of preterm neonates admitted to neonatal intensive care unit (NICU), in one of two patterns: early-onset thrombocytopenia and late-onset thrombocytopenia **(Chakravorty *et al.*, 2005).**

Thrombocytopenia has been used as an early but non-specific marker for sepsis **(Benjamin *et al.*, 2000).** An earlier study demonstrated evidence of a relationship between Gram-negative infections and thrombocytopenia **(Guida *et al.*, 2003).**

Aim of the work

This work aimed to:

1. Assess platelet count in preterm neonates with culture proved sepsis.
2. Study the relationship between different infectious

agents (gram positive, gram negative bacteria and fungi) and thrombocytopenia.

2. Patients and Methods

Patients:

This study comprised 40 preterm neonates admitted to the NICU of Menofyia University hospital during a period of one year from April 2007 to April 2008.

Patients group:

A: Patients classified regarding body weight according to Saiman et al.(2000) :

Group (1): 25 newborns with low birth weight (LBW) < 2500 gm, (12 males and 13 females).

Group (2): 12 newborns with VLBW < 1500 gm, (6 males and 6 females).

Group (3): 3 newborns with ELBW < 1000 gm, (2 males and 1 female).

B: Patients classified regarding onset of sepsis according to Gonzalez et al.(2003) :

Group (a): 13 newborns with early onset sepsis (EOS)(in the first 3 day of life) (5 males and 8 females).

Group (b): 27 newborns with LOS (after 3 days of life)(15 males and 12 females).

C: Patients classified regarding platelet count according to Bussei et al.(2005):

Group (I): 13 newborns with mild thrombocytopenia (platelet count≤ 150,000/ mm3) (10 males and 3 females).

Group (II): 19 newborns with moderate thrombocytopenia (platelet count ≤ 100.000/ mm3) (6 males and 13 females).

Group (III): 8 newborns with severe thrombocytopenia (platelet count ≤ 50,000/ mm3) (4 males and 4 females).

Inclusion criteria:

1. Any preterm, delivered in our hospital, admitted to NICU and develop septicemia.
2. Normal platelet count in first day of life.
3. Negative drug history.

Exclusion criteria:

1. Infant of hypertensive mother.
2. Preterm with birth asphyxia.
3. Neonatal alloimmune thrombocytopenia.
4. Neonatal autoimmune thrombocytopenia.
5. Necrotizing enterocolitis.
6. Infant with dissminated intravascular coagulopathy (DIC).
7. Preterm with congenital malformation, congenital infection and/or inborn error of metabolism.
8. Infant with surgical problem.

Methods:

All newborns were subjected to :

a) Full history taking including prenatal, natal and post natal history.

b) Thorough clinical examination.

c) Close monitoring for sepsis (clinical sepsis score, hematological sepsis score and blood culture).

d) Laboratory diagnosis of DIC by DIC score (**Taylor *et al.*, 2001**).

Specimen collection

From every patient 4 - 4.5cc of blood was collected by a venipuncture needle under complete aseptic condition and was used as follows:

1) 1-1.5 cc of blood was put in a vacuette tube containing EDTA (K3E-EDTA K3; Greiner bio-one) for doing complete blood film in first day of life and again when baby develop sepsis.
2) One cc of blood was inoculated using a signal blood culture system (oxoid) on blood culture bottles for bacteria and fungi and incubated at 35 -37 °C.
3) two cc of blood in vacutte tube containing citrate for doing prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level and fibrin marker [fibrin degradation products (FDPs) and D-Dimer].

3. Results

Table (1): Distribution of data among studied groups according to the medical history.

Medical history	No	%
Maternal risk factors:		
PROM	6	15%
Free	34	85%
Delivery modes:		
NVD	15	37.5%
CS	25	62.5%
Sex:		
Male	20	50%
Female	20	50%
APGAR (1m) $\overline{X}$ ± SD	6.62 ± 0.77	
Range	(7– 10)	
Resuscitation		
Usual resuscitation	26	65
O_2 inhalation	14	35
Gestational age(Wks): $\overline{X}$ ± SD	32.52 ± 1.92	
Range	(28 – 35)	
Wight: $\overline{X}$ ± SD	1.77 ± 0.47	
Range	(0.80 – 2.5)	
Weight groups		
LBW	25	62.5%
VLBW	12	30%
ELBW	3	7.5%
Post natal age(days) $\overline{X}$ ± SD	18.77 ± 7.67	
range	(13- 60)	
Special intervention		
HB + NCPAP	11	27.5%
Photo + NCPAP	6	15%
Photo	7	17.5%
IMV & NCPAP + photo	6	15%
Free	10	25%
NS onset		
early	13	32.5%
late	27	67.5%
DIC score		
PT (80% -100% of control)	96 ± 3.75	
aPTT(25-35 second)	28.6 ± 3.15	
Fibrinogen (200-400 mg/ dl)	294± 21.91	

FDP (7.7 ug/ ml) D-Dimmer(250 ng/ml)	7.8± 0.64 201.6± 8.16	
Prognosis Recovery Death	 29 11	 72.5% 27.5%

NVD : Normal vaginal delivery

CS: Caesarean section PROM: Premature rupture of membrane.
HB: Head Box Photo : Phototherapy
NCPAP: Nasal Continuous Positive Airway Pressure
IMV : Intermetaed mandatory ventilation.

Table(2): Blood culture(Type of organisms) among studied group.

Type of organism:		No	%	Total	Percent
Gram +ve	Staph	1	2.5%	4	10%
	Non hemolytic strept	1	2.5%		
	Strept	2	5%		
Gram –ve	Klebsilla	16	40%	18	45%
	Citobacter	2	5%		
Fungal	Candida	11	27%	13	32.5%
	Asprigillus	2	5%		
Mixed	Fungal + (G-ve)	3	7.5%	5	12.5%
	Fungal + (G+ve)	1	2.5%		
	(G +ve) + G -ve)	1	2.5%		

Table (3): Comparison among the weight groups as regarding the parameters of hematological sepsis score.

Hematological sepsis score	LBW n=25		VLBW n=12		ELBW N=3		P value
	± SD $\overline{X}$		± SD $\overline{X}$		± SD $\overline{X}$		
TLC	10.96±8.93		9.25±6.9		5.6±2.34		>0.05
ANC	6.22±5.9		4.73±5.45		3.2±1.85		>0.05
Immature PMN	0.14±0.4		0.19±0.3		0±0		>0.05
Mature PMN	5.7±5.8		4.5±5.2		3.2±1.85		>0.05
I/T	0.02±0.04		0.04±0.07		0±0		>0.05
I/M	0.01±0.03		0.05±0.09		0±0		>0.05
Platelet count ($\times 10^9$)	101.24±49.04		71.17±28.3		48± 0.35		< 0.05
Degenerative change (Toxic granule)	No. 15	% 60%	No. 9	% 75%	No. 1	% 33.3%	>0.05

Table (4): Comparison between early onset & late onset sepsis regarding parameters of hematological sepsis score

Parameter of hematological sepsis score	Early onset (n=13)		Late onset (n=27)		P value
	± SD $\overline{X}$		± SD $\overline{X}$		
TLC	6.45 ± 4.3		11.7 ± 8.8		>0.05
ANC	3.6 ± 3.9		6.4 ± 6.05		>0.05
Immature PMN	0.0046 ± 0.011		0.26 ± 0.41		< 0.05
Mature PMN	3.027 ± 3.058		6.08 ± 5.97		>0.05
I/T	0.01 ± 0.03		0.03 ± 0.06		>0.05
I/M	0.01 ± 0.03		0.03 ± 0.07		>0.05
Platelet count ($\times 10^9$)	130 ± 42.8		72.3 ± 30.9		<0.001
Degenerative changes (Toxic granule)	No. 4	% 30.8%	No. 21	% 77.8%	<0.05

Table (5): Comparison among type of organism and parameters of hematological sepsis score.

Hematological sepsis score	Gram +ve (n=4)	Gram –ve (n=18)	Fungal (n=13)	Mixed (n=5)	P value kruskol walls test
	± SD $\overline{X}$	± SD $\overline{X}$	± SD $\overline{X}$	± SD $\overline{X}$	
Post natal age	4.5 ± 2.6	6 ± 6.1	13.6 ± 9.3	9.4 ± 3.2	>0.05
TLC	10.05+ 7.1	10.06 ± 8.2	17.9 ± 9.5	12.2 ± 8.7	< 0.05
ANC	3.5 ± 1.9	4.2 ± 4.8	6.4 ± 4.5	9.7 ± 10.1	>0.05
Immature PMN	0.00 ± 0.00	0.13 ± 0.35	0.18 ± 0.38	0.50 ± 0.37	>0.05
Mature PMN	2.5 ± 2.2	3.8 ± 4.5	6.2 ± 4.5	9.1 ±9.7	>0.05
I/T	0.00 ± 0.004	0.008 ± 0.026	0.028 ± 0.06	0.11 ± 0.06	< 0.001
I/M	0.00± 0.02	0.01 ± 0.04	0.03 ± 0.08	0.01 ± 0.06	< 0.05
Platelet count ($\times 10^9$)	158.7 ± 68.1	112.6 ± 19.3	52.6 ± 16.2	51.2 ± 19.5	< 0.001
Degenerative changes (Toxic granule)	No. % 2 50%	No. % 9 50%	No. % 9 69.2%	No. % 5 100%	>0.05

Table(6): Comparison between prognosis and parameters of hematological sepsis score and blood culture.

Hematologic sepsis score	Recovery (n=29)		Death (n=11)		P value
	$\overline{X}$ ± SD		$\overline{X}$ ± SD		
TLC	10.3 ± 9.01		9.5 ± 6.04		> 0.05
ANC	6.49 ± 4.82		5.53 ± 4.50		> 0.05
Immature PMN	0.18 ± 0.38		0.18 ± 0.32		> 0.05
Mature PMN	4.2 ± 4.8		3.9 ± 4.02		> 0.05
I/T	0.02 ± 0.03		0.05 ± 0.04		> 0.05
I/M	0.01 ± 0.04		0.03 ± 0.05		> 0.05
Platelet count ($\times 10^9$)	96.24 ± 47.17		77.4 ± 33.35		< 0.05
	No.	%	No.	%	
Degenerative change (Toxic granule)	17	58.6%	8	72.7%	>0.05
Blood Culture					
Gram +ve	4	13.8%	0	0%	>0.05
Gram –ve	16	55.2%	2	18.2%	
Fungal	5	17.2%	8	72.7%	
Mixed	4	13.7%	1	9.1%	

Table (7) Comparison between degree of thrombocytopenia and all parameters

	Mild thrombocytopenia (n=13)		Moderate thrombocytopenia (n =19)		Severe thrombocytopenia (n=8)		P
GA	$\overline{x}$ ± SD		$\overline{x}$ ± SD		$\overline{x}$ ± SD		≤ 0.05
	33.83 ± 1.69		32.21 ± 1.65		31± 1.51		
	No	%	No	%	No	%	
Weight							
LBW	11	44	12	48	2	8.0	<0.05
VLBW	2	16	7	58.3	3	25.6	
ELBW	0	0	0	0	3	100	
Onset of sepsis							
EOS	5	38.5	6	46.2	2	15.4	> 0.05
LOS	8	29.6	13	48.1	6	22.2	
Type of Organism							
gram +ve	3	75	1	25	0	0	< 0.05
gram -ve	2	11.1	14	77.8	2	11.1	
fungal	5	38.5	3	23	5	38.5	
mixed	3	60	1	20	1	20	
Hematological	$\overline{x}$ ± SD		$\overline{x}$ ± SD		$\overline{x}$ ± SD		
TLC	11.82 ± 9.6		7.22 ± 5.47		13.90 ± 9.13		>0.05
ANC	6.37 ± 5.88		3.68 ± 3.79		8.65 ± 7.37		>0.05
Immature PMN	0.21 ± 0.41		0.20 ± 0.40		0.087 ± 0.13		>0.05
Mature PMN	6.16 ± 5.67		3.18 ± 3.77		8.28 ± 6.99		>0.05
I/T	0.028 ± 0.06		0.01 ± 0.048		0.046 ± 0.07		>0.05
I/M	0.01 ± 0.04		0.02 ± 0.05		0.05 ± 0.09		>0.05
Degenerative	No	%	No	%	No	%	
	8	61.5	11	57.9	6	75	>0.05
Out come	No	%	No	%	No	%	
Recover	9	31	15	51.7	5	17.2	>0.05
Death	4	36.4	4	36.4	3	27.3	

4. Discussion

NS is a significant cause of morbidity and mortality in the newborns, particularly among preterm LBW infants (**Bizzarro *et al.*, 2005).**

No single laboratory test has been found to have acceptable specificity and sensitivity for predicting infection. The current gold standard for confirming the diagnosis of NS is isolation of the causal organism by blood culture. However blood culture results are not available until 24-48hr after staining the culture (**Layseca-Espinosa *et al.*, 2002)**.

Eighty five percent of our patients delivered spontaneously without any risk factors, this result in agreement with **Kaufman *et al.*, 2001** who reported that spontaneous preterm deliveries account for 64 to 75% of all preterm deliveries.

However, PROM accounted for 15% of risk factor for preterm labor. This result comes in concordance with **Guibourdenche *et al.*, 2002** who

reported that PROM accounted for 7.1 % to 51.2% of all preterm deliveries. Also, **Hashim *et al.*, 2004** and **Abou-Hussein *et al.*, 2005** reported, maternal history of prolonged PROM was present in 25% of all preterm deliveries.

There was a statistically significant decrease in platelet count with decrease in gestational age of the infants. The gestational age of neonates with severe thrombocytopenia was lower than those with moderate and mild thrombocytopenia. These result in concordance with other result reported by **Beiner *et al.*, 2003** who mentioned that the degree of thrombocytopenia in neonates had a significant lower average of gestational age at delivery. So screening these high-risk groups for thrombocytopenia might be beneficial in terms of early diagnosis and management. **Pherson and Juul**, **2005** reported that the risk of thrombocytopenia changed with corrected gestational age and appear to vary inversely with increasing gestational age.

Platelet count was significantly lower in ELBW than VLBW and LBW. This result agrees with **Beiner *et al.*, 2003** who reported that birth weight was statistically significant low among thrombocytopenic neonates a specially severe thrombocytopenia in ELBW.

Early onset sepses(EOS) comprised 32.5 % while late onset sepses (LOS) comprised 67.5 %. Also **Abdel Hady and Zaki (2003)** reported that EOS is 31% and LOS is 69% of patients.

There was statistically significant decrease in platelet count in LOS than in EOS, this may be due to gram –ve and/or fungal infection as the majority of those who develop LOS had gram –ve and/or fungal infection. There was an increase in the remaining hematological sepsis score in LOS but this increment is of no statistically significant difference when compared with EOS. These results are matching with **Hashim *et al.*, 2004 and Abou Hussein *et al.*, 2005** as they reported that, platelet count was statistically significant high in patient with EOS . However **Peterec *et al.*, 1996** reported that normal platelet count doesn't exclude neonatal sepsis. Also **Gonzalez *et al.*, 2003** reported that the use of platelet count is of limited value in establishing the diagnosis of infection in neonates.

The majority of our patients had gram –ve infection followed by fungal infection. Also **Abdel – Hady and Zaki, 2003** reported that, klebsilla was found in 41.3 % of patients, *Staph aurous* in 10.3% of patients, enterobacter in 3.4 % of patients. Also **Badrawi *et al.*(2005** reported that klebsiella 63.6%, enterobacter 7.8 % and streptococci 2.8 % of septic group. **Hashim *et al.*, 2001 , Hashim *et al.*, 2004** and **Iskender and Morcos, 2006** reported that klebsilla was considered the most common organism isolated from blood culture and leading infectious agent in their study. The high incidence of klebsilla was due to its presence in the delivery room suction apparatus and its incidence diminished after meticulous sterilization.

In the present study candida comprised 27% and aspergillus 5%. This in agreement with **Guida *et al.*, 2003** who mentioned that candida species are the most frequently isolated fungal pathogens. **Benjamin *et al.*, 2003** also found that the incidence of candidemia in neonates is 4% to 15%. **Cotton *et al.*, 2006** also reported that candidiasis incidence ranged from 2.4% to 20.4 %. **Lupetti *et al.*, 2002** reported that candida species are the fourth most commonly recovered organisms from all blood cultures of hospitalized individuals.

Newborns with gram –ve infection had mild thrombocytopenia while newborns with fungal and mixed infection had moderate thrombocytopenia. Newborns with fungal and mixed infection their hematological sepsis score show marked increase in all parameters except platelet count.

Platelet count showed a statistically significant decline in those who died than those who recovered, inspite its count was moderately deficient in both groups. This agree with **Vanderschueren *et al.*, 2000** and **Strassus *et al.*, 2002** who reported that mortality was higher with drop of platelet count. Also **Parker, 2002** reported that the modest increase in platelet count during NICU admission translated to a decreased risk of death.

The incidence of mild thrombocytopenia is 32.5%, moderate thrombocytopenia 47.5% and severe thrombocytopenia 20% among our patients.This result agrees with that reported by **Levi, 2005** who mentioned that the incidence of mild thrombocytopenia is 35-44%, moderate thrombocytopenia 20 -25 % and severe thrombocytopenia 12-15% among NICU patients. Also **Murray *et al.*, 200** found that 6% of neonates in NICU had severe thrombocytopenia. **Roberts** and **Murray, 2001** they also reported that 20% of thrombocytopenia in NICU patients was severe.

Christensen *et al.*, 2006 observed thrombocytopenia among ELBW neonates at a rate more than twice that reported among the general NICU population, the causes of thrombocytopenia were small for gestational age or delivered to a hypertensive mother, DIC, bacterial infection, fungal infection and necrotizing enterocolitis, respectively.

Torres *et al.*, 2007 retrospectively reviewed the medical charts of 42 neonates with LOS with positive blood culture. The gestational age of newborn at birth was 31±4.9 (24-41.5 weeks), with a mean birth weight 1,618 ± 911 grams (750-4,0709). No significant differences were found except for birth

weight, days of stay in the NICU, thoractomy, days of mechanical ventilation, antibiotic therapy before sepsis and thrombocytopenia. The incidence of thrombocytopenia was significantly higher in candida sepsis than in bacterial sepsis (100% vs 5.9%) (P< 0.001). Thrombocytopenia is a highly specific reliable marker of neonatal candida sepsis.

Bhat *et al.*, (2009) found thrombocytopenia in very LBW babies with sepsis, organism- specific platelet response is seen (the frequency and duration of thrombocytopenia were more with gram –ve and fungal infections). In addition multi-organ failure and death are more in these babies, and survival decrease with the increases severity and duration of thrombocytopenia, with prolonged ventilation and increased need for platelet transfusion. In contrast with **Manzoni *et al.*, 2009** reports, thrombocytopenia might not be an organism- specific marker of sepsis. Caution should be maintained in relating a low platelet count to any infectious agent (or group of agents) in preterm VLBW neonates.

Conclusion

Severe thrombocytopenia in young gestational age, ELBW and fungal infection. There is a relationship between fungal infection and thrombocytopenia. Thrombocytopenia can be used as an early diagnostic marker for sepsis and a prognostic one. Candidemia and delay to appropriate therapy contribute to increased morbidity and mortality.

Recommendation

Effective steps towards infection control in delivery room and neonatal unit.

Fluconazol has been recommended as prophylaxis against systemic fungal infection in extreme low birth weight infants.

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