Prognostic Value of Platelet Count in Paediatric Intensive Care Unit

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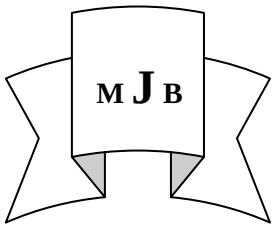

Abstract

Background: Thrombocytopenia is commonly observed in critically ill patients. A low platelet count is a strong and independent predictor of an adverse outcome in critically ill patients, thereby facilitating a simple and practical risk assessment in these patients and potentially guiding the use of complex or expensive treatment strategies.

Objectives: To evaluate the variation in platelet counts and the risk factors associated with thrombocytopenia and mortality in pediatric intensive care patients.

Patients and Method: A prospective, observational cohort study was undertaken in the Pediatric Intensive Care Unit of Babylon Gynecology and Pediatric teaching hospital in Hilla city, Babil, Iraq over a period of 5 months from 1st May 2011 to 1st October 2011. Besides patients' demography, source of admission, primary diagnosis, presence or absence of sepsis, bleeding, use of central venous or arterial lines and mechanical ventilation were recorded. Laboratory data collected at admission included complete blood counts, C- reactive protein, blood urea nitrogen and serum creatinine, serum bilirubin and coagulation profile. These were also repeated with the occurrence of thrombocytopenia. Platelet count was performed daily for all patients.

Results: The median Pediatric Intensive Care Unit stay was 4 days (range 2-98 days). At least one episode of thrombocytopenia was seen in 58 patients (44.61%) Mild, moderate, and severe thrombocytopenia was present in 27.69%, 23.07%, and 14.61%, of patients respectively. Sepsis, high blood urea and serum creatinin, high total serum bilirubin, and positive C-reactive protein had significant correlation with the development of thrombocytopenia. There was a significant association between mortality and the presence of mechanical ventilation, sepsis, blood transfusion, high blood urea and serum creatinin, positive CRP, and leukocytosis. The survivors had higher platelet counts throughout the Pediatric Intensive Care Unit stay and after an initial fall in platelet counts showed a significantly higher rise in the platelet counts in the following days than the non-survivors.

Conclusions:

- Thrombocytopenia is common in pediatric intensive care unit especially in patients with sepsis and coagulation defect.
- Thrombocytopenic children have higher incidence of bleeding, and higher mortality.
- Any drop in platelet counts even without thrombocytopenia needs an urgent and extensive evaluation.
- Serial measurements of platelet counts are better predictors of pediatric intensive care outcome than one-time values.
- Thrombocytopenia is common in ICUs and constitutes a simple and readily available risk marker for mortality, independent of and complementary to established severity of disease indices. Both a low nadir platelet count and a large fall of platelet count predict a poor vital outcome in adult ICU patients.
- We did not study the mechanisms that lead to decreased platelet count. Nevertheless, we think other studies provide compelling arguments to assume that inflammation-induced platelet sequestration plays a major role.

Keywords: Platelets, mortality, pediatric intensive care. thrombocytopenia , coagulopathy.

القيمة التنبوئية لعدد الصفائح الدموية في وحدةِ العنايةِ المركّزة للأطفالِ

الخلاصة

خلفية الدراسة: يُلاحظُ نقص الصفائح الدموية عموماً في المرضى الذين هم في حالة خطرةٍ. يعد نقص الصفائح الدموية متنبأ قويا ومستقلا للنتائج المعاكسة في المرضى الذين هم في حالة خطرةٍ، مما يُسهّل بشكل بسيط وعملي تقدير الخطر في هؤلاء المرضى مم يمكن من استخدام إستراتيجياتِ معالجةِ غاليةٍ أو معقّدةٍ.

الأهداف: لتَقييم الاختلاف في عدد الصفائح الدموية وعوامل الاختطار المصاحبة بنقص الصفائح الدموية والوفيات في وحدةِ العنايةِ المركّزة للأطفالِ.

المرضى وطريقة العمل: دراسة مجموعة ملاحظاتية متابعة أجريت في وحدةِ العنايةِ المركّزة للأطفالِ في مشفى بابل التعليمي للنسائية والأطفال في مدينة الحلة– بابل– العراق على مدى خمسة أشهر للفترة من الأول من أيار ٢٠١١ إلى الأول من تشرين أول ٢٠١١. إضافة إلى الدراسة الإحصائية السكانية للمرضى ، تم تسجيل مصدر إدخال المرضى، التشخيص الأولي، وجود التسمّمِ أو عدمه، النزف، استعمال الأوردة والشرايين المركزيةِ والتهويةِ الميكانيكيةِ . جمعت البيانات المخبرية لدى دخول المرضى وتَضمّنتْ حساب دَمَّ كاملَ، سي بروتين التفاعلي، اليوريا النتروجيني في الدم ، الكرياتنين المصلي، مادة الصفراء المصلية ولمحة من عوامل التخثر. أعيد إجراء هذه التحاليل عند حصول حالة نقص في الصفائح الدموية. اجري فحص عددي يومي للصفائح الدموية لجميع المرضى.

النتائج: ان متوسط مدة البقاء في وحدة العناية المركزة للأطفال كانت 4 أيام وبمدى98–2 يوما. سجلت حالة نقص بالصفائح الدموية لمرة واحدة على الأقل في 58 مريضا (44.6%). وجد أن نقص الصفائح الدموية البسيط والمتوسط والشديد في ,27.69% 14.61% ,23.07% وعلى التوالي. هنالك ارتباط معنوي هام بين قلة الصفائح الدموية و حالات التسمم، ارتفاع نسبة اليوريا في الدم والكرياتنين المصلي والمادة الصفراء المصلية وال سي بروتين التفاعلي. وجد ترافق معنوي بين الوفيات والتهويةِ الميكانيكيةِ، التسمم، نقل الدم، ارتفاع نسبة اليوريا في الدم والكرياتنين المصلي وال سي بروتين التفاعلي وازدياد عدد كريات الدم البيضاء. كان لدى الباقين على قيد الحياة من المرضى عدد أعلى من الصفائح الدموية طيلة فترة البقاء في وحدة العناية المركزة للأطفال و قد اظهر المرضى الأحياء الذين كان لديهم نقص في الصفائح الدموية ارتفاعا ملحوظا في عدد الصفائح مقارنة بالمرضى الذين فارقوا الحياة.

الاستنتاجات:

- نقص الصفائح الدموية حالة شائعة في وحدة العناية المركزة للأطفال وخصوصا لدى المرضى الذين يعانون من التسمم واعتلال تخثر الدم.
- للمرضى الذين لديهم نقص في الصفائح الدموية معدل حدوث أعلى للنزف والوفاة.
- إن أي هبوط في عدد الصفائح الدموية حتى وان لم يصل العدد إلى حالة نقص الصفائح الدموية ، فهو بحاجة إلى تقييم مستعجل وشامل.
- تعد المقاييس المتسلسلة لعدد الصفائح الدموية متنبأ أفضل لتحديد المصير في وحدة العناية المركزة للأطفال مقارنة بالقياس لمرة واحدة.
- نقص الصفائح الدموية شائع في وحدة العناية المركزة ويعتبر مؤشر خطورة بسيط ومتوفر لقياس الوفاة، غير معتمد ومكمل لمعرفة شدة مؤشرات المرض،كليهماالمستوى الأدنى الطبيعي للصفائح الدموية وهبوط كبير في عددها سوف يتوقع مصير سيء في وحدة العناية المركزة للبالغين.
- نحن لم ندرس الميكانيكية التي ادت الى نقص الصفائح الدموية ولهذا نحن نعتقد يجب ان تكون هناك دراسات اخرى توفر حجة مكملة لأدراك ان الألتهاب الذي يحفزحصر الصفائح الدموية يلعب دورا مهما.

الكلمات المفتاح: الصفائح الدموية، الوفيات، وحدة العناية المركزة للأطفال، نقص الصفائح الدموية، اعتلال تخثر الدم.

Introduction

Thrombocytopenia is a common laboratory abnormality in critically ill patients. [1] A low platelet count not only may represent a diagnostic clue for the cause of the underlying disease or complicating circumstance but can also be used as a strong predictor of an adverse outcome. Critically ill patients often

present with thrombocytopenia. [2] The incidence of thrombocytopenia (platelet count<150x109/L) in critically ill medical patients is 35 to 44%. [3–5] A platelet count of <100x109/L is seen in 20 to 25% of patients, whereas 12 to 15% of patients have a platelet count <50x109/L. In surgical and trauma patients, the incidence of thrombocytopenia is higher with 35 to 41% of patients having less than 100x109/L platelets.[6,7] Typically, the patient's platelet count decreases during the first 4 days in the intensive care unit (ICU).[8] Thrombocytopenia is a well known complication in intensive care unit (ICU) patients. It has been associated with various risk factors, but mainly with sepsis [4,6,7]. The platelet count, which was related only with homeostasis disorders, is now considered to be a predictor of outcome in the ICU setting as an independent parameter.[3] It is found to be as good a predictor as the various mortality scores used in the ICU. [9] This is attributed to the important role played by platelets in the inflammatory process apart from their role in thrombus formation. [10] The advantage of using platelets as a predictor of ICU outcome is the dynamic nature of daily platelet counts which takes the disease progression into account in contrast to various mortality scores which use only the worst parameters within first 24h after admission or at admission.[3] Various adult studies have shown an initial decrease in platelet count followed by increase, but no such study has been carried out in critically ill children.(8,11,12) In particular, sustained thrombocytopenia over more than 4 days after ICU admission or a drop in platelet count of >50% during ICU stay is related to a 4- to 6-fold increase in mortality .[3]

Aims: To evaluate the variation in platelet counts and the risk factors associated with thrombocytopenia and mortality in pediatric intensive care patients.

Patients and Methods

A prospective, observational cohort study was undertaken in the Pediatric Intensive Care Unit (PICU) of Babylon Gynecology and Pediatric teaching hospital in Hilla city, Babil, Iraq over a period of 5 months from 1st May 2011 to 1st October 2011. Thrombocytopenia was defined as a platelet count of < 150.0/nL. It was categorized depending on the severity as mild, moderate, severe or very severe on the basis of platelet counts below 150.0/nL, 100.0/nL, 50.0/nL or 20.0/nL, respectively. All consecutively admitted patients staying for 48h or more in the PICU over a period of 5 months were included in this study. The patients were followed-up prospectively. Besides patients' demographical data, source of admission, primary diagnosis, presence or absence of sepsis, bleeding, use of central venous or arterial lines and mechanical ventilation were recorded. Laboratory data collected at admission included complete blood counts (CBC) obtained by auto- hematology analyzer (Diagon), C- reactive protein (CRP) done by serological kit, blood urea nitrogen (BUN) and serum creatinine were done either manually or by strip(Reflotron), serum bilirubin done by bile- meter , and coagulation parameters(prothrombin time partial thromboplastin time). These were also repeated with the occurrence of thrombocytopenia. If any patient had platelet counts done more than once in 24h, the lowest value was recorded for analysis.Platelet count was performed daily for all patients. Low platelet counts were confirmed by direct examination of the blood smear. Chi-

square test was used to measure the strength of association between the factors considered and the dependent variable. P-value < 0.05 was considered significant.

Results

Out of the 220 total admissions in PICU during the study period, 130 patients who remained in the unit for at least 48h were recruited in the study (Table 1), where their age ranging between 1 day- 9 years with Mean ± SD of 54.76 ± 77.4 months with M:F ratio of 2.03:1. The source of admission was mainly from hospital wards and emergency department, 43.8% and 36.9% respectively. Respiratory failure is the main admission category 57.7%. Most patients 56.2% had been stayed for < 7 days in the PICU. The most common risk factors for outcome(table 3) were mechanical ventilation, sepsis, positive c-reactive protein(CRP), total leucocytes count(TLC > 15000) and blood urea nitrogen (BUN > 20 mg/dl), 68.46%, 37.69%, 30.76%, 23.07% and 21.53% respectively. The survival rate was 46.92%. At least one episode of thrombocytopenia was seen in 58 patients (44.61%), eight patients (6.15%) of them had thrombocytopenia on admission; the rest had developed it during the course of PICU stay. Mild, moderate, and severe thrombocytopenia was present in 27.69%, 23.07%, and 14.61% of patients respectively. About 56.2% of the patients staying in PICU for less than 7 days had at least one episode of thrombocytopenia. Patients with PICU acquired thrombocytopenia had statistically significant lower baseline (platelets count were low normal side). Age, gender, source of admission, admission category, PICU long stay, total leukocytes count , the use of arterial venous catheters, and mechanical ventilation had no significant correlation with the development of thrombocytopenia. Sepsis, high blood urea nitrogen and serum creatinine, high total serum bilirubin, and positive CRP had significant correlation with the development of thrombocytopenia as shown in Table 2. There was a significant relation between mortality and the presence of mechanical ventilation, sepsis, blood transfusion, high blood urea and serum creatinine, positive CRP, and leukocytosis. There was no significant difference in mortality with age, gender, source of admission, admission category, PICU long stay, and the use of arterial or venous catheters or bleeding as shown in Table 3. The presence of thrombocytopenia was associated with increased mortality (79.31% *vs.* 31.94 %, P -value < 0.001). The mortality was significantly higher with lower platelet counts on day four and day seven and lower nadir platelet counts irrespective of the presence of thrombocytopenia. Platelet counts were lower in the non-survivors than survivors throughout the ICU stay. The admission platelet counts were lower in non-survivors than in survivors. (56.2%) patients stayed in the PICU for less than 7 days, and in this group the mortality was 56.6%. Platelet counts decreased significantly in the initial 4-7 days of PICU stay in both survivors and non-survivors. In non-survivors the platelets counts did not rise significantly after the first week as compared to the survivors. A drop of > 50% from the baseline platelet counts increased the mortality. Survivors had a mean drop of 8% (range 0-29.6%) compared to 83% (range: 27-85%) in non-survivors from the baseline (P<0.00). On day seven, 20 (34.48%) patients had thrombocytopenia and the mortality in this group was 90%. Normal platelet counts on admission were associated with better survival

than normal platelet counts on day 4 and day 7 ($P<0.05$).

Table 1 Demographic parameters of eligible patients admitted to pediatric intensive care unit (PICU) (n=130)

Parameters		NO.	%
Age			
	Range	1 day- 9 years	
	Mean ± SD	54.76 ± 77.4 months	
Gender	Male	87	66.9
	Female	43	33.1
	M:F	2.03:1	
Source of admission	Emergency Unit	48	36.9
	Hospital wards	57	43.8
	Operation theatre	11	8.5
	Others	14	10.8
Admission Category	Neurological	22	16.9
	Monitoring	13	10.0
	Circulatory Failure	6	4.6
	Respiratory Failure	75	57.7
	CPR*	14	10.8
PICU stay	< 7 days	73	56.2
	7-14 days	33	25.4
	> 14 days	24	18.5
Risk factors	Mechanical ventilation	89	68.46
	Sepsis	49	37.69
	Coagulation parameters disorders	10	7.69
	Bleeding	10	7.69
	Blood transfusion	10	7.69
	BUN** > 20 mg/dl	28	21.53
	S. creatinine >1.2 mg/dl	23	17.69
	TSB*** > 1mg/dl	12	9.23
	Positive CRP****	40	30.76
	TLC***** > 15000/mm^3	30	23.07
	TLC < 4000/mm^3	23	17.69
Outcome	Died	69	53.07
	Survive	61	46.92

*Cardio pulmonary resuscitation, ** Blood urea nitrogen, ***Total serum biluribin, **** C-reactive protein, *****Total Leukocytes count.

Table 2 Clinical parameters associated with thrombocytopenia

Parameters	Patients with thrombocytopenia (n=58)		Patients with no thrombocytopenia (n=72)		P- value
	NO.	%	NO.	%	
Age Range	1 day-7.3 years		1 day-9 years		
Median	30 day		36 day		
Mean ± SD	44.66 ±63.14 months		54.76 ±77.40 months		
Gender Male	38	65.5	49	64.5	0.38
Female	20	34.5	23	30.3	0.64
M:F	1.9:1		2.1:1		
Source of admission					
Emergency unit	21	36.2	27	35.	0.38
Hospital wards	22	37.9	35	5	0.85
Operating theatre	6	10.3	5	46.	0.78
Others	9	15.5	5	1	0.28
				6.6	
				6.6	
Admission Category					
Neurological	9	15.5	13	17.1	0.29
Monitoring	5	8.6	10	13.2	0.52
Circulatory Failure	4	6.9	2	2.6	0.41
Respiratory Failure	34	58.6	41	53.9	0.41
CPR*	8	13.8	6	7.3	0.59
PICU stay					
<7 days	29	50.0	44	57.9	0.07
7-14 days	16	27.6	17	22.4	0.86
>14 days	13	22.4	11	14.5	0.68
Risk factors					
Mechanical ventilation	41	70.6	48	66.66	0.45
Sepsis	35	60.34	14	19.44	0.002
Coagulation parameters	7	12.06	3	4.16	0.20
defect	7	12.06	3	4.16	0.20
Bleeding	7	12.06	3	4.16	0.20
Blood Transfusion	23	39.65	5	6.94	0.0006
BUN** > 20 mg/dl	20	34.48	3	4.16	0.0003
S. creatinine>1.2 mg/dl	10	17.24	2	2.77	0.02
TSB*** > 1mg/dl	30	51.7	10	13.8	0.001
Positive CRP****	20	34.48	10	13.8	0.06
TLC***** > 15000/mm^3	13	22.41	10	13.8	0.5
TLC < 4000 /mm^3					
Outcome Died	46	79.31	23	31.94	0.005
Survive	12	20.68	49	68.05	0.000

*Cardio pulmonary resuscitation, ** Blood urea nitrogen, ***Total serum biluribin, **** C-reactive protein, *****Total Leukocytes count.

Table 3: Clinical parameters associated with outcome

Parameters	Survivors (n=61)		Non survivors (n=69)		P- value
	No	%	No	%	
Gender Male	36	60.0	50	72.5	0.13
Female	24	33.3	19	27.5	0.44
Source of admission					
Emergency Unit	22	36.7	25	36.2	0.74
Hospital wards	27	45.0	30	43.5	0.69
Operating theatre	7	11.7	4	5.8	0.36
Others	4	6.7	10	14.5	0.10
Admission Category					
Neurological	10	17.4	12	16.7	0.66
Monitoring	11	18.3	2	2.9	0.01
Circulatory Failure	3	5.0	3	4.3	1.00
Respiratory Failure	31	51.7	43	62.3	0.16
CPR*	5	8.3	9	13.0	0.28
PICU median stay					
< 7 days	34	56.7	39	56.5	0.55
7-14 days	17	27.8	16	23.2	0.86
>14 days	10	16.7	14	20.3	0.41
Risk factors					
Mechanical ventilation	34	55.73	55	79.7	0.02
Sepsis	14	22.95	35	50.72	0.002
Coagulation defect	3	4.91	7	10.14	0.20
Bleeding	3	4.91	7	10.14	0.20
Blood Transfusion	2	3.27	8	11.59	0.05
BUN** > 20 mg/dl	5	8.19	23	33.33	0.00
S. creatinine>1.2 mg/d	3	4.91	20	28.98	0.00
TSB*** > 1mg/dl	3	4.91	9	13.04	0.08
Positive CRP****	10	16.39	30	43.47	0.001
TLC***** > 15000/mm^3	9	14.75	21	30.43	0.02
TLC < 4000/mm^3	8	13.11	15	21.73	0.14

*Cardio pulmonary resuscitation, ** Blood urea nitrogen, ***Total serum biluribin, **** C-reactive protein, *****Total Leukocytes count.

Discussion

The relationship between drop in platelets counts during PICU and mortality in critically ill patients was analyzed in this study. In a large group of medical and surgical ICU patients the prognostic importance of platelet counts (PC) extends well beyond initial changes. With regard to PC, day 2 after ICU admission can be viewed as a turning point [11].

A total of 58- patients (44.6%) had at least one platelet count <150 × 10^9/L, this incidence of thrombocytopenia and PICU acquired thrombocytopenia is comparable to Strauss *et al*, Shruti Agrawal *et al*, and Vanderschueren S, et al studies [3,5,18] where 44%, 25%, and 41.3 of the patients acquired thrombocytopenia while in the ICU respectively. The incidence of thrombocytopenia has ranged from 13-58% in various studies. [5,13] The difference in the ranges can be explained by the differences in study population and different inclusion criteria and definitions used in various studies [18]. The incidence of platelet counts <100x10^9/L in our study was 23.7%, which is comparable to Shruti Agrawal *et al* study 23.2 [18]. 22% in a neonatal ICU, [14, 15], 22% in medical-surgical ICU [3] and 21% in a non-coronary medical ICU.[5]

Sepsis was also found to have an association with thrombocytopenia 60.34% (35 of 58) as compared to 65 % of the patients with sepsis had thrombocytopenia (23 of 49) in Shruti Agrawal, Anil Sachdev et al study[18] , which is comparable to other adult studies. [3,4,16]

Coagulation defect was not significant factor associated with thrombocytopenia, which is comparable to the significant association of DIC in the evolution of thrombocytopenia found by Strauss *et al*. [5] Monitoring as admission category was a low risk factor for development of thrombocytopenia. Disturbed biochemical markers in the form of elevated blood urea nitrogen, serum creatinine, bilirubin, positive CRP which identifies sicker patients, were also predictive of thrombocytopenia. Invasive intravascular catheters (arterial or venous) and mechanical ventilation have been described in the literature as an independent risk factor for development of thrombocytopenia, though this may only reflect the disease severity and local ICU preferences[5,17] In our study, there was no such association observed. This may be due to small patient number. Mechanical ventilation, Sepsis, Transfusion, BUN > 20 mg/dl S. creatinine >1.2 mg/d, Positive CRP, and TLC > 15000 was found to be significantly associated with mortality as has been found in other studies [5] Bleeding can be both a risk factor and cause for thrombocytopenia and this was not elaborated sufficiently in the present study, though most of the patients had bleeding secondary to thrombocytopenia rather than vice-versa.

This study had some limitations. Besides small sample size, various confounding factors are present at any given point of time in critically ill children, which cannot be controlled. Many pre-existing conditions and drugs in use may influence the platelet counts, which were not studied in this cohort. The limited number of patients in certain groups does not allow great precision in the estimation of odds ratio and this may have missed some important risk factors. There are no similar pediatric studies to compare the data with, though there are a few neonatal studies done on the incidence and prognostic value of low platelet counts on admission. [14, 15] The studies on thrombocytopenia in pediatric ICU are few and the ones which have been done have very different objectives than our study rendering it difficult to compare the present work with any pediatric study. [8] So the results need to be validated in a larger cohort.

Conclusions and Recommendation

- Thrombocytopenia is common in pediatric intensive care unit especially

in patients with sepsis and coagulation defect.

- Thrombocytopenic children have higher incidence of bleeding, and higher mortality.
- Any drop in platelet counts even without thrombocytopenia needs an urgent and extensive evaluation.
- Serial measurements of platelet counts are better predictors of pediatric intensive care outcome than one-time values.
- Late thrombocytopenia is more predictive of death than early thrombocytopenia.

- Similar studies are required with larger number of patients in the pediatric age group to further consolidate the present study's findings.
- Thrombocytopenia is common in ICUs and constitutes a simple and readily available risk marker for mortality, independent of and complementary to established severity of disease indices. Both a low nadir platelet count and a large fall of platelet count predict a poor vital outcome in adult ICU patients.
- The study is not powered to actually work out the cause and effect and can only suggest an association between various factors.
- We did not study the mechanisms that lead to decreased platelet count. Nevertheless, as pointed out above, we think other studies provide compelling arguments to assume that inflammation-induced platelet sequestration plays a major role.

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