

Research Article

Thrombocytosis in Febrile Illness in Children of Age Three Months to 14 Years at a Tertiary Care Hospital of Nepal

Sajan Kumar Thakur¹, Pramod Kattel^{*2}

National Medical College and Teaching Hospital, Birgunj, Nepal

¹Lecturer, Department of Paediatrics, Kathmandu National Medical College, Kathmandu, Nepal

²Lecturer, Department of Obstetrics and Gynaecology, Kathmandu National Medical College, Kathmandu, Nepal

ABSTRACT

Background and Objectives: Acute febrile illness is common presentation in children. Thrombocytosis can be used as a predictor of febrile illness in children. The objectives of this study were to find out the prevalence and causes of thrombocytosis among febrile children and to assess the utility of platelet count as a potential predictor of serious bacterial infection alone or in association with other predictors.

Material and Methods: A cross-sectional descriptive study was done in 290 febrile children following convenience sampling method. Statistical analysis was done using SPSS. Univariate analysis using chi-square test for categorical and independent samples and “t” test for continuous variables were done.

Results: Thrombocytosis was present in 13.1% of cases. Most cases had mild thrombocytosis (10%) whereas moderate thrombocytosis was present in 2.8% of cases and 0.3% cases had severe thrombocytosis. Lymphocyte level, erythrocyte sedimentation rate and C-reactive protein also showed a significant association with thrombocytosis ($p < 0.05$). Serious bacterial infection was present in 209 cases out of which 30 children had thrombocytosis but was not significant compared to children with non serious bacterial infection with thrombocytosis ($p = 0.171$).

Conclusion: Thrombocytosis was found to have an association with febrile illnesses. More so, it indicated a fair discriminate ability to diagnose infectious cause of disease. However there was no statistical significance between thrombocytosis and serious bacterial infection.

Keywords: Children, Febrile illness, Tertiary care, Thrombocytosis.

INTRODUCTION

Acute febrile illness has been defined as elevation of temperature $>38^{\circ}\text{C}$ in children

between three months to 14 years of age [1]. Most common cause of febrile illness in children is upper respiratory tract infection (URTI) [2]. Infectious and non infectious

diseases will also present as common causes of febrile illness. Febrile illnesses in children are meningitis, acute gastroenteritis (AGE), lower respiratory tract infections (LRTIs), osteomyelitis, urinary tract infections (UTIs), sepsis, enteric fever and other infectious diseases. Rheumatological diseases and malignancy will also present as febrile illness in children [3].

Thrombocytosis refers to a platelet count more the normal value. The normal platelet counts ranges from 1.5 to 4.5 lakhs/l. High platelet counts may result both thrombotic and hemorrhagic complications [4] which is more common in primary thrombocytosis [5]. Platelets express CD154 that directly stimulates endothelial cells to initiate inflammation at the vessel wall, which helps in clinical contribution of platelets in inflammatory diseases. However, to date only correlative data have been published linking platelets to clinical inflammatory conditions. Platelets express functional CD154 [6], with implied function in inflammation. Though, there are conflicting reports of association of thrombocytosis with different types of infection, some authors have shown associations with severe bacterial infections [7].

The purpose of the study was firstly to find the incidence of thrombocytosis in children with febrile illness with or without severe infection. Secondly, it could be based as sepsis screen singly or in combination with other predictors to predict severity of infection.

MATERIAL AND METHODS

This is a cross-sectional descriptive study conducted at Department of Paediatrics at National Medical College and Teaching

Hospital (NMC-TH), Birgunj, Parsa, Nepal on infants and children (three months-14years) over a period of one year from August 2015 to August 2016. A total of 290 patients were enrolled in the study. Convenience sampling method was used to enroll the cases in this study till all required sample size was fulfilled.

Children from three months to 14 years of age with temperature $>38^{\circ}\text{C}$ (Axillary) were included. Children with malnutrition, haemolytic anemia, malignancies, rheumatological diseases or chronic inflammatory diseases and those who received antibiotics or vaccination within 48 hours of presentation were excluded. The parents of patients were explained in detail about the nature of the study. Written informed consent was obtained from parents before including them in study. A detailed history and clinical evaluation of the patients were carried out. All patients with suspected sepsis had evaluation of white blood cell (WBC) count, platelet count, blood culture, urine microscopy and culture as required. Lumbar puncture for cerebrospinal fluid (CSF) analysis and culture, as well as stool routine and culture and chest radiographs were obtained as required.

The CBC was quantified using fully automatic complete analyzer, Nihon Kohden Celltac E with five differential parts and 22 parameters. Blood cultures were done in different media and/or glucose broth. Urine was obtained by clean catch method. Urine, CSF and stool cultures were done using standard laboratory techniques. For those who had financial constraint, the tests were done without any charge. They were helped by college charity and also at personal level. Those who were kept in hospital for longer

period, their bed charges were waived out for academic purpose.

The obtained data were entered into computer program Microsoft Office Excel 2007. Statistical analysis was done using Statistical Package for Social Sciences (SPSS), Version 16.0. Univariate analysis was done using chi-square test for categorical and independent samples and "t" test for continuous variables. Confidence level of the study was kept at 95%, hence a "p" value less than 0.05 indicated a statistically significant association.

Operational definitions

Infection: Infection is the invasion of body tissues by disease causing agents, their multiplication and the reaction of host tissues to these organisms and the toxins they produce [8].

If any of the mentioned parameter of total leukocyte count (TLC), differential leukocyte count (DLC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Widal test, Peripheral blood smear (PBS) for Malaria, Mantoux test, abnormal chest X ray findings was/were positive along with clinical suspicion then infection was said to be present.

Serious bacterial infection: It is defined as meningitis, sepsis, bone and joint infections, urinary tract infections, pneumonia and enteritis [3].

Sepsis: It is defined as systemic inflammatory response system (SIRS) in response to an infectious process [9].

Meningitis: It is an acute inflammation of the protective membranes covering the brain and

spinal cord, collectively known as the meninges [1].

Pneumonia : It is an inflammatory condition of the lung affecting primarily the microscopic air sacs known as alveoli [10] along with cough and/or difficult breathing with or without fever, chest indrawing with or without fast breathing or abnormal chest x-ray (consolidation, streaky infiltrate, pneumatocele, pleural effusion, pneumothorax).

Enteritis: It is an inflammation of the small intestine [10] with three or more liquid or semi liquid stools per 24 hour or ~~one or more~~ bloody stools.

Thrombocytosis: Platelet count of more than 5 lakhs/cu mm and is graded as Mild: 5-7 lakhs/cu mm; Moderate: 7-10 lakhs/cu mm and Severe: >10 lakhs/cu mm.

Septic Screen: It is an investigation that is carried out in children who have fever more than 38°C and includes hemoglobin, TLC, neutrophil, lymphocyte, eosinophil, monocyte, ESR and CRP as required.

RESULTS

A total of 290 children admitted to Department of Pediatrics, Birgunj with body temperature (Axillary) >38°C meeting selection criteria were analyzed for demographic details. Male patients were in majority (71%) as compared to females (29%). Study population included children from age of three months to 14 years. Major percentage of study population was in age group of six months to one year (22.8%) followed by children of age group one to three years [Table 1].

Majority of cases had platelet count within normal range (86.9%). However, 13.1% cases had thrombocytosis. Most of the thrombocytosis cases had mild thrombocytosis (10%). Moderate thrombocytosis was present in 2.8% of cases and 0.3% cases were with severe thrombocytosis [Table 2].

Table 1. Distribution of Subjects according to Demographic characteristics (N=290)

SN.	Features	Cases	
		No.	Percentage (%)
1.	Gender		
	Male	206	71
	Female	84	29
2.	Age		
	0-6 months	52	17.9
	6-12 months	66	22.8
	1-3 Yrs	61	21
	3-6 Yrs	49	16.9
	6-9 Yrs	24	8.3
	9-12 Yrs	24	8.3
	>12 Yrs	14	4.8

Table 2. Distribution of Subjects according to category of Platelet count (N=290)

SN	Platelet count	Cases	
		No.	Percentage (%)
1.	Normal	25	86.9
		2	
2.	Thrombocytosis	38	13.1
	Mild	29	10
	Moderate	8	2.8
	Severe	1	0.3

Association of thrombocytosis with haematological findings among febrile children was sought. Significantly higher

proportion of thrombocytosis patients as compared to normal patients were CRP positive (27.2% vs 72.8%), thus showing a significant association between CRP positivity and thrombocytosis (p=0.001). Similarly, other investigation such as Widal test, PBS for Malaria parasite and Mantoux test does not show a significant association with thrombocytosis [Table 3].

The cases were combined to see presence of infection. The presence of infection was seen in 81% of normal cases and 92.1% of cases with thrombocytosis. The presence of infection was not significantly associated with thrombocytosis (p=0.092) [Table 4].

Children with infection were classified into two categories based on thrombocytosis. Thrombocytosis was seen in 44.7% of patients with pneumonia but other infections such as scrub typhus, enteric fever, AGE, bronchiolitis and others were observed among non thrombocytotic cases [Table 5].

Serious bacterial infection was seen in 209 children and among them 30 children had thrombocytosis. In group with children of non serious bacterial infection, only eight children had thrombocytosis. There was no significant association between patients with thrombocytosis and serious bacterial infection [Table 6].

DISCUSSION

Febrile episodes are quite common in children throughout the world. However, they are often manifestations of underlying pathology that is much diversified and might have variable prognosis.

For proper management and prognosis of febrile illness of children, it is essential that the underlying pathology is diagnosed early

Table 3. Outcome of different Investigations for presence of Infection

SN	Investigations	Normal		Thrombocytosis		Statistical significance	
		No.	%	No.	%	χ^2	p
1.	CRP positive	75	72.8	28	27.2	27.8	0.001
2.	Widal positive	16	100	0	0	2.89	0.089
3.	Malaria parasite	1	100	0	0	0.15	1
4.	Mantoux positive	1	33.3	2	66.7	3.62	0.057

Table 4. Association of Platelet with Infection (N= 290)

Infection	Normal (n=252)		Thrombocytosis (n=38)		Statistical significance	
	No.	%	No.	%	χ^2	p
Present	204	81.0	35	92.1	2.834	0.092
Absent	48	19.0	3	7.9		

Table 5. Association of Platelet with Specific type of Infection

S.N.	Specific type of Infection	Normal (n=252)		Thrombo-cytosis (n=38)	
		No.	%	No.	%
1	Sepsis	15	6.0	4	10.5
2	Scrub typhus	8	3.2	0	
3	Mesenteric lymphadenitis	2	0.8	1	2.6
4	Enteric fever	19	7.5	0	
6	Febrile convulsion	12	4.8	2	5.3
7	AGE	25	9.9	0	
8	Meningitis	15	6.0	4	10.5
9	UTI	9	3.6	5	13.2
10	Bronchiolitis	12	4.8	2	5.3
11	Pneumonia	87	34.5	17	44.7
12	Others	48	19.0	3	7.9

and precisely. The evaluation of a child with febrile illness and with no obvious focus of infection is a challenging task and can be expensive, time consuming and may need invasive tests. The general condition of the infant can be deceptive and does not assist reliably in clinical differentiation of a low risk versus high risk bacterial infection [11].

This is compounded by the fact that no single laboratory test has been shown to identify infants with sepsis. Laboratory markers which have been used to predict sepsis include raised WBC counts, CRP, Procalcitonin (PCT) and interleukin-6 levels. WBC count, though easily available and widely used as a predictor of sepsis, by itself, does not compare well with relatively more recent markers like CRP and PCT [12].

>400,000/ μ L have been documented in 3% to 15% of pediatric patients [13]. Thrombocytosis in paediatric age group is invariably due to an underlying cause such as acute infection, chronic inflammation, childhood malignancies, iron deficiency anemia and chronic hemolytic states. Primary or essential thrombocytosis is extremely rare. Infections of the respiratory tract, urinary tract, gastrointestinal tract, the bones and meninges are the most common causes of reactive thrombocytosis. Platelet counts in most cases range between >500,000/ μ L to 700,000/ μ L, but in 6-8% of children may range between >700,000/ μ L to 1,000,000/ μ L and in 2-3% patients, the counts can be markedly elevated (>1,000,000/ μ L). Higher counts are more common in neonates and

Table 6: Association of Platelet with Serious Bacterial Infection

	Serious Bacterial Infection	Non serious bacterial infection	Statistical significance	
			χ^2	P
Thrombocytosis	30	8	1.874	0.171
Normal	179	73		
Total	209	81		

Recently, the focus has shifted to other cost-effective, easily available and adequately precise indicators that can help in understanding the underlying pathology behind febrile illnesses in children. Platelet count is one of such indicators that are being explored for their utility in this context. Availability of automated hematology analyzers give results of platelet counts as a part of the routine hematology work-up with a dependable degree of accuracy. Thrombocytosis with platelet counts

infants [14]. Platelet count has not been extensively evaluated as a predictor of sepsis among febrile children. The present study tries to fill that gap specially in context with a low resource setting like ours where facilities for assessment of advanced biomarkers such as CRP, PCT and interleukin-6 levels are neither universally available nor affordable and the focus is generally on development of new diagnostic methods which apart from being adequately precise should also be cost-effective and universally available. Hence, the present study was planned and carried out to

observe the incidence of thrombocytosis in children with febrile illness with or without severe infection and to evaluate whether it can be used as a basis for sepsis screening singly or in combination with other predictors to predict severity of infections.

In our study majority of children enrolled were males. Prevalence of males over females depicts both the declining sex ratio as well as secondary status of females in our society [15]. The gender wise discrimination of the children continues even before birth and continues throughout the life, and utilization of health care services is another example of this continued discrimination as evident in a low sex ratio in present study. Majority of children with febrile illnesses were aged up to three years (61.7%). Febrile illness in children younger than 36 months is common and has potential serious consequences [16]. Most of the hospital admissions among children in this age group are attributable to febrile illnesses and our study also showed that significantly higher proportion of patients were in this age group, thus underscoring the fact that febrile illnesses in this age group are common and are a major contributory factor towards burden of hospital admissions.

Although, a number of studies have discussed the thrombocytosis under primary and secondary types [5,17,18]. This finding is in agreement with the observations of Chiarello et al [19] who reported mild thrombocytosis to be present in 72-86%, moderate in about 6-8%, and severe thrombocytosis in 0.5-3% of children.

Our study had higher percentage of children with respiratory disease. In a previous study in Nepalese children with acute lower respiratory tract infection, Malla et al [20]

have indicated low haemoglobin levels to be a risk factor for acute LRTIs accompanied with fever as a clinical manifestation.

However, platelet count was found to be significantly higher in febrile children. Platelet count has been taken to be an indicator of infectious reason of fever with varying sensitivity and specificity for different infectious etiologies.

Wolach et al [21] showed raised platelet counts to be an indicator of severe bacterial infection. Similar observations were also made by other workers in children with severe LRTIs [22], severe bacterial infection [4] and H. influenza meningitis [23]. However, in a study by Chandra et al [24], it was indicated that low platelet count was an indicator of acute malarial infection in patients presenting with fever as the clinical manifestation. They reported the sensitivity of the test to be 87.2% and specificity to be 65% using cut-off value <1.5 lakhs/cu mm. Similar results were obtained by Jeremiah et al [25] among children with asymptomatic malaria. In present study too, we evaluated the diagnostic efficacy of platelet count as an indicator of fever with infectious origin but at a different cut-off level.

Kubota et al [26] also evaluated the utility of platelet count as an indicator of early stage of respiratory tract viral infection and found association with different causative agents of viral infection like respiratory syncytial virus -RSV, influenza, measles, adenovirus or human herpes virus 6.

The mean platelet count was significantly higher in RSV patients than in patients with other respiratory infections. These findings indicate that the assumption of platelet count

as an indicator of fever with infectious origin has limitations and needs to be addressed differently in combination with other clinical variables [27].

In present study, mild to moderate thrombocytosis was found to be present in 12.8% of cases. As stated above, platelet count as such and thrombocytosis in particular is a predictor of variable health conditions and a derangement might be associated with an altered health condition of an individual. The prevalence of thrombocytosis has been reported to be ranging from 6 % to 15% among hospitalized children [18].

In present study, it was assumed that thrombocytosis was a result of infectious origin of the disease. In previous assessment, Fouzas et al [17] also have reported that thrombocytosis in combination with elevated CRP may help in early recognition of febrile young infants at risk for severe bacterial infections. On evaluating the incidence of thrombocytosis among different tests carried out to evaluate infectious etiology, only CRP showed a statistically significant association with thrombocytosis. With other tests, the prevalence of thrombocytosis was low.

Malaria as stated earlier is marked by thrombocytopenia and not thrombocytosis, hence low prevalence of thrombocytosis in malaria positive group is justified. Although thrombocytosis is a finding associated with pulmonary tuberculosis yet its prevalence is often seen to be incremental with initiation of treatment [28].

Moreover, Mantoux test used for evaluation of tuberculosis and Widal test used for typhoid are quick diagnostic tests having variable accuracy [29,30] hence the results

indicated by these tests might be false positive as well as false negative, thus affecting the association with thrombocytosis.

In present study, an attempt was also made to evaluate the role of platelet count as a predictor of serious bacterial infection alone or in association with other predictor parameters. In order to search for other indicators that can contribute towards improvement of these criteria, age less than three years, TLC, ESR and CRP were found to be significantly associated with higher infection rate. Serious bacterial infection was found in 209 children.

Thrombocytosis was seen among 30 children with serious bacterial infection. There was no statistical significant difference between children with thrombocytosis and serious bacterial infection. However, thrombocytosis was found in higher proportion of children with serious bacterial infection compared to children without serious bacterial infection.

The findings of present study try to explore the relationship between hematological changes especially that of platelet count with febrile illness patients in context of infectious origin and reveal that a combination of easily measurable clinical and laboratory parameters will help in understanding the origin of disease.

In order to restrain the rampant use of antibiotics, the findings of present study are helpful in providing useful judgement for treating paediatrician in the management of febrile illnesses avoiding inadvertent use of antibiotics. The findings in present study are thus very useful from clinical practice point of view and need elaboration in variable set up to make it widely applicable.

CONCLUSION

On the present study, febrile illnesses in pediatric patients were more common in younger age group. Majority of subjects with febrile illness were males.

Thrombocytosis was seen in higher percentage in children with serious bacterial infection compared to non serious bacterial infection however it was not statistically significant. Thus, there is clinical evidence to justify the use of thrombocytosis as the marker of febrile illness in children. Thrombocytosis was found in all children with infection; however infection was also present in children without thrombocytosis.

This study showed association of thrombocytosis with acute febrile illness and its utilization in serious bacterial illnesses. This study will help in the menace of indiscriminate use of antibiotics and provide physicians a basis for decision-making in judicious use of antibiotics for the management of childhood febrile illnesses. Further studies are warranted to corroborate the findings of the present study

LIMITATIONS

All patients presenting with febrile illness could not be categorized despite exhaustive investigations available at our center. Children with reactive thrombocytosis could not be ascertained whether they had preceding thrombocytosis. Only a few set of investigations were done in every patient as part of study.

Children presenting with fever were studied, however infection can also present without fever and might have thrombocytosis. Study

was done at center with small study population belonging to fixed geographical area with homogenous ethnicity, so further study is necessary for generalization.

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AUTHOR'S CONTRIBUTION

SKT & PK- Planning, Research and preparation of manuscript

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Correspondence to:

Dr. Pramod Kattel

Lecturer

Dept. of Obstetrics and Gynaecology,
Kathmandu National Medical College,
Kathmandu, Nepal,

E-mail: pramodkattel85@gmail.com