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RESEARCH ARTICLE

THROMBOCYTOSIS AS A PREDICTOR AND DIAGNOSTIC TOOL FOR SERIOUS BACTERIAL INFECTION IN FEBRILE INFANTS; SRINAGAR, INDIA.

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Abstract

Introduction: To estimate the incidence of Reactive Thrombocytosis among febrile young infants and to assess the utility of platelet count as a potential predictor and diagnostic tool of serious bacterial infection (SBI).

Methods and Materials: This study was conducted as a prospective non-randomized study between March 2016 to Feb 2018 at the tertiary care pediatric unit, Srinagar, India. Inclusion criteria were all infants 30 to 89 days of age, admitted with rectal temperature>38°C/100.4°F without an apparent focus of infection on history and clinical examination. Exclusion criteria were infants having fever more than 72 hours and who had received antibiotics or vaccination within 48 hours of presentation. Also, the results of the sepsis evaluation on admission were recorded. SBI included all cases of occult bacteremia, urinary tract infection, bacterial meningitis, pneumonia, bacterial gastroenteritis and infections of the soft tissues and bones.

Results: Of the 298 infants studied, 78 (26.2%) had SBI. Platelet count was significantly higher in infants with SBI compared to those without {Platelet count ≥ 4 lakhs /mm3 in SBI (84.6%) vs. Non-SBI (42.4%). Mean platelet count 5.1 ± 1.1 in SBI vs. 3.9 ± 1.6 in Non-SBI which was statistically significant (P<0.05). Thrombocytosis had a moderate ability in predicting SBI [Area under curve area under the curve: 0.760]. The combination of platelet count ≥450,000/mm3, WBC ≥15,000/mm3, C-reactive protein ≥2 mg/dl and pyuria ≥5 White blood cells (WBC) per High power field (HPF) resulted in misclassification of only 2 infants with SBI (5.1% of SBIs).

Conclusions: Reactive thrombocytosis was a frequent finding in young infants with SBI. Thrombocytosis ≥450,000 cells/mm3, in combination with leukocytosis, elevated C-reactive protein (CRP) and pyuria, may help in early recognition of febrile young infants at risk for SBI.

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Introduction:-

Fever is one of the most common conditions requiring the attention of the pediatrician. The evaluation of an infant with febrile illness and no obvious focus of infection is a challenging task and can be expensive, time-consuming and invasive. The general condition of the infant can be deceptive and does not assist reliably in clinical differentiation of low risk versus high-risk bacterial infection. This is compounded by the fact that no single laboratory test has been shown to identify infants with serious bacterial infection (SBI). Laboratory markers which have been used to predict SBI include raised white blood cell (WBC) counts, C-reactive protein (CRP), procalcitonin (PCT) and even interleukin-6 levels. WBC count, though easily available and used widely as a predictor of SBI, by itself, does not compare well with relatively more recent markers like CRP and PCT. Availability of automated hematology analyzers gives results of platelet counts as a part of the routine hematology work-up, with a dependable degree of accuracy.

Thrombocytosis an elevation in the peripheral blood platelet count to values more than 4 lakh/mm3 is common in infancy and childhood occurring in 3 to 13% of children. Reactive Thrombocytosis seems to affect up to 15% of hospitalized children. It's more common in neonates, particularly premature ones and up to 2 years of age. Febrile infants less than 3 months of age present a management challenge, as many of these have no identifiable source of fever, and the prevalence of serious bacterial infection (SBI) in this age group is high. The most commonly suggested strategy is for the febrile neonates to be admitted to a hospital and undergo full sepsis workup.

In the past decade, several management strategies based on the combination of physical and laboratory findings have been proposed, but no protocol has been universally adopted. Furthermore, a series of laboratory parameters such as White blood cell (WBC) count, absolute neutrophil count, pyuria, C-reactive protein (CRP), and more recently, interleukin-6 and procalcitonin, have been extensively evaluated and compared as potential predictors of SBI. However, these laboratory tests lack the adequate predictive ability and the idea of a simple, rapid and inexpensive diagnostic test that could accurately identify bacterial infections among febrile infants remains unattainable (1-32).

Methods and Materials: -

We followed the cases of all infants aged 30 to 89 days, admitted to G.B Pant Children Hospital associated with Government Medical College Srinagar a tertiary care pediatric hospital in Srinagar district, northern India (Figure.1), from March 2016 to Feb 2018 for investigation of fever (defined as rectal temperature >38°C) without a focus of infection. Infants who had a fever for more than 72 hours, and had received antibiotics or vaccination were excluded.

All patients who fulfilled the inclusion criteria underwent sepsis evaluation including WBC count, platelet count, blood culture, urine microscopy and culture and serum CRP levels. Lumbar puncture for Cerebrospinal fluid (CSF) analysis and culture, pleural tap for pleural fluid analysis as well as stool culture and chest radiographs, were obtained at the discretion of the attending pediatrician.

The WBC count with differential and the platelet count were quantified using automated laboratory equipment (Sysmex KX 21).
Blood cultures were monitored by an automated system (BacT/ALERT 3D). Urine was obtained by urethral catheterization using a sterile technique. The WBCs in the urine were quantified by standard microscopic examination and expressed as WBC >5 per high power field (HPF) in a centrifuged sample or >10 leucocytes/mm3 in an uncentrifuged sample (17). The urine, CSF, pleural and stool cultures were monitored using standard laboratory techniques.

Fig.1: Study area

Serious bacterial infection was defined as occult bacteremia, Urinary tract infection, pneumonia, bacterial enteritis and infection of soft tissue or bones. Isolates such as Staphylococcus epidermidis in the blood culture were considered contaminants unless they were isolated from more than two consecutive cultures.

Urinary tract infection was defined as a single known pathogen on urine culture with ≥1000 Colony-forming units (CFU) /ml of urine obtained by urethral catheterization. The diagnosis of UTI is based on culture of properly collected specimen Urinalysis is helpful in providing immediate information to suspect UTI and enable initiation of treatment.

Confirmation of the diagnosis on urine culture is necessary pneumonia was defined as the presence of a focal infiltrate on chest radiographs plus any of the following signs; a positive blood culture for a pathogenic organism or culture of a pathogenic organism from the pleural fluid sample. Occult bacteremia was defined as pure growth of a single pathogenic micro-organism on blood culture of a febrile young infant without any apparent focus of infection on history and clinical examination. Probable bacteremia was defined as the growth of two or more types of bacteria (19). Definite bacterial meningitis was defined as isolation of organism on Cerebrospinal fluid (CSF) culture. Probable bacterial meningitis was defined as abnormal CSF on analysis with sterile CSF culture. Only patients with definite bacterial infection were taken as serious bacterial infection.

Results: -

This study was conducted in the Department of Physiology in collaboration with G.B Pant children Hospital Srinagar, India for a period of 2 years. The total number of admissions of patients with fever without an apparent source of infection admitted to hospital was 360. The total number of patients fulfilling the inclusion criteria was 298. 62 patients were excluded out of 360 as 24 of these had a fever for more than 72 hours, 6 had recent vaccination history, and 32 were treated with antibiotics within 48 hours of presentation.

Results showed out of the 298 infants which fulfilled the inclusion criteria, SBI was documented in 78 (26.2%). Of these, 32 (41.0%) had UTI (22 with Escherichia coli), 16 occult bacteremia (4 with Klebsiella, 6 with Methicillin-resistant Staphylococcus aureus, 6 with Staphylococcus aureus), 18 infants had pneumonia, and 12 were diagnosed with bacterial meningitis (4 with E. Coli, 4 with Group B Streptococcus and 4 with methicillin-resistant Staphylococcus Aureus). Two infants had positive blood as well as urine cultures for Escherichia coli. None of the infants had a positive stool culture there was no case of bacterial pneumonia positive for blood culture.

The remaining 220 infants (73.8%) with negative sepsis evaluation were categorized in the Non-SBI group (Table.1).

Table 1: -Depicting Serious Bacterial Infection Across Diagnosis

Serious Bacterial Infection across diagnosis	Percentage
Pneumonia	23.1
Meningitis	15.4
Occult Bacteremia	20.5
Urinary Tract Infection	41.0

Age, gender and residence were non-significant across both SBI and Non-SBI groups. P-value non-significant (P> 0.05). Thrombocytosis (Platelet count more than 4 lakh/mm3) was significantly higher in SBI, 66 out of 78 vs. Non-SBI 120 out of 220 (P <0.05), CRP and Total leukocyte count (TLC) was significantly high on SBI than Non-SBI (P<0.05).

Blood culture was positive in 18 SBI patients, Urine culture 32, Cerebrospinal fluid (CSF) culture in 12, Chest x-ray (CXR) for pneumonia and pleural fluid analysis /culture for isolation of pathogen for pneumonia in 18 patients (Tables.2-5).

Table 2: - Comparing various SBI and non SBI Variables

	SBI	Non SBI	P-value
Temperature(°F)	103 ±1.3 (101,105)	102 ±1.1 (101,105)	0.000
Hemoglobin	11.8±2.7 (9.2, 19.2)	12.0 ±2.3 (8.6, 19)	0.72
Total Leukocyte count (000's/mm3)	14,915±4998 (5900,24500)	10,948±4586 (5200,29000)	0.000
Total Platelet Count (lakh/mm3)	5.1± 1.1 (1.5 ,7.2)	3.9±1.6 (0.4,7.4)	0.000

Temperature, TLC and total platelet count were higher in the SBI group than in Non-SBI (P<0.05) (Table.3) Shows the Mean ±1 SD (lowest and highest variable across each investigation).

Table 3: - The mean platelet count in lakhs/mm^3 across SBI and Non SBI

Pneumonia	4.7 lakh/m33
Bacterial meningitis	5.2 lakh/mm3
Occult bacteremia	4.9 lakh/mm3
UTI (urinary tract infection)	5.3 lakh/mm3
Non -SBI	3.9 lakh/mm3

Table4: Depicting investigations across SBI And Non-SBI

Investigations	SBI%	Non SBI%
Thrombocytosis >4 lakh/mm3	84.6	54.5
CRP(≥2mg/dl)	51.3	13.6
Total Leukocyte Count(≥15,000/mm3)	51.3	21.8
Urine examination for pus cells(>5/HPF)	64.1	5.5
Platelet count≥ 4.5 lakh/mm3	82.1	30.0

Table 5: Test characteristics for differential platelet count threshold

Platelets in lakh/mm3	N (78)	Sensitivity %	Specificity %	PPV%	NPV%	Accuracy %	OR %
≥4.0 lakh/mm3	66	84.6	45.5	35.5	89.3	55.7	4.6
≥4.5 Lakh/mm3	64	82.1	70	49.2	91.7	73.2	10.7
≥5.0 lakh/mm3	40	53.8	70.0	38.9	81.1	65.8	2.7
≥6.0 lakh/mm3	16	20.5	90.0	42.1	76.2	71.8	2.3

According to test characteristics for different platelet count thresholds we came to know that platelet count of≥ 4.5 lakh/mm3 carried best accuracy of 73.2 %, odds ratio of 10.7, sensitivity 82.1%, specificity 70%, Negative predictive value (NPV) 91.7% and Positive predictive value PPV) 49.2% than any other platelet threshold, so the platelet count of ≥4.5 lakh/mm3 had a differential tendency to pick up the maximum patients out of SBI and lesser patients out of Non SBI (Table.6)

Table 6: Depicting combined high-risk criterion of TLC, Pyuria, CRP and Platelet count in early prediction of patients of SBI

Variables	N (78)	Sensitivity %	Specificity %	PPV %	NPV%	OR
TLC	40	51.3	78.2	45.5	81.9	3.8
Pyuria ≥5 wbc/hpf	50	64.1	94.5	80.6	8.1	30.9
CRP	40	51.3	86.4	57.1	83.3	6.7
Plt Count (≥4.5 lakh/mm3)	64	82.1	70.0	49.2	91.7	10.7
TLC+Pyuria	64	82.1	76.4	55.2	92.3	14.8
TLC+Pyuria+CRP	70	89.7	68.2	50.0	94.9	18.7
TLC+Pyuria+CRP+Platelet (≥4.5 lakh/mm3)	74	94.9	53.6	42.0	96.7	21.4

PLT: Platelet count; CRP: C-reactive protein; HPF: High power field, PPV: Positive predictive value; NPV: Negative predictive value.

A combined high-risk criterion of two tests (15,000/mm3 for WBC and ≥5WBC/HPF of pyuria, led the misclassification of 17.9 % of the SBIs (14 infants), while 52 infants were falsely classified as high-risk out of Non-SBI.A further combination of WBC ≥15000 /mm3, pyuria≥10 WBC /HPF, and CRP ≥2 mg/dl, led to the misclassification of 4 infants with SBI (10.2% of SBI), whereas 70 infants without bacterial infection were falsely classified as high-risk. The addition of platelet count of ≥ 4.5 lakh/mm3 to the above combination of three tests resulted in misclassification of only 4 SBI infants (5.1%) with improvement of picking up 4 more patients with SBI over the combination of three tests, with final pick up of 64 out of 78 SBI patients thus the combination of four tests may help in early prediction of serious bacterial infection in febrile young patients.

Discussion:-

This study was conducted in the Department of Physiology in collaboration with G.B Pant Children Hospital, a referral tertiary care hospital associated with Government Medical College, for children of Kashmir valley. The study was conducted from March 2016 to Feb 2018. The total number of admissions during the period was 54678. The total number of patients with fever without an apparent focus of infection on history and clinical examination admitted during this period was 360. Finally, the total number of patients fulfilling the inclusion criteria was 298.

The purpose of this study was, to estimate the incidence of reactive thrombocytosis among febrile young patients and to assess the utility of platelet count as a potential predictor of serious bacterial infection. The prevalence of SBI in our population was 26.2% (78 out of 298 patients were positive for SBI). Since the study was conducted in a tertiary care hospital, to which more sick patients are referred, it can be the reason for the high prevalence of SBI in our study.

In this study, platelet count was significantly higher in febrile infants with documented bacterial infection, particularly in those with UTI, occult bacteremia and pneumonia. However, due to a substantial overlap, it was difficult to identify threshold value that could clearly differentiate infants with SBI from other febrile infants. Platelet counts of ≥450,000/mm3 had the highest accuracy (73.2%) in differentiating infants with SBI, with less false negative and false positive results. The overall ability of platelet count to identify infants with SBI was moderate (AUC 0.76), but comparable to the other parameters.

The fact that platelets can behave like an acute phase reactant is well recognized. Stimulation of platelet production is triggered by interleukin-6 which enhances megakaryopoiesis directly and indirectly by stimulating hepatic thrombopoietin production. In this study, platelet count was significantly higher in infants with SBI compared to those without, and this was so, reactive thrombocytosis in combination with WBC, CRP and pyuria seem to be a useful tool in predicting early the risk of SBI in young febrile patients. Hence, thrombocytosis in febrile young infants could be used as a quick inexpensive diagnostic tool for predicting SBI.

Conflict of interests:
None

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References:-

1. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. Pediatrics 1990;85: 1040-1043.
2. Hsiao AL, Baker MD. Fever in the new millennium: a review of recent studies of markers of serious bacterial infection in febrile children. Curr Opin Pediatr 2005; 17: 56-61.
3. Mantadakis E, Tsalkidis A, Chatzimichael. A: Thrombocytosis in childhood. Indian Pediatr 2008; 45: 669-677.
4. Sutor AH. Thrombocytosis in childhood. Semin Thromb Hemost1995;21: 330-9.
5. Kaushansky K. Thrombopoietin: the primary regulator of platelet Production. Blood 1995; 86:419-31.
6. Ishiguro A, Suzuki Y, Mito M, Shimbo T, Matsubara K, Kato T, et al. Elevation of serum thrombopoietin precedes thrombocytosis in acute infections. Br J Haematol 2002; 116: 612-18.
7. Fujiwara T, Harigae H, Kameoka J, Yokoyama H, Takahashi S, Tomiya Y, et al. A case of familial thrombocytosis: possible role of altered thrombopoietin production. Am J Hematol 2004; 76: 395-7.
8. Kikuchi M, Tayama T, Hayakawa H, Takahashi I, Hoshino H, Ohsaka A. Familial thrombocytosis. Br J Haematol 1995; 89:900-902.
9. Williams EC, Shahidi NT. Benign familial thrombocytosis. Am J Hematol 1991; 37: 124-5.
10. Fernandez-Robles E, Vermylen C, Martiat P, Ninane J, Cornu G. Familial essential thrombocythemia.Pediatr Hematol Oncol 1990; 7: 373-6.
11. Hasle H.Incidence of essential thrombocythemia in children. Br J Haematol 2000; 110: 751.
12. Yang RC, Qian LS. Essential thrombocythaemia in children: a report of nine cases. Br J Haemato12000; 110: 1009-10.
13. Papageorgiou T. Theodoridou A. Kourti M, Nikolaidou S, Athanassiadou F, KaloutsiV.Childhood essential thrombocytosis. Pediatr BloodCancer 2006; 47: 970-1.
14. Dror Y, Blanchette V S. Essential thrombocythaemia in children. Br J Haematol 1999; 107: 691- 698.
15. Dror Y, Zipursky A, Blanchette VS. Essential thrombocythemia in children. J Pediatr Hematol Oncol 1999; 21: 356- 63.
16. Yohannan MD, Higgy KE, al-Mashhadani SA, Santhosh Kumar CR. Thrombocytosis Etiologic analysis of 663 patients. Clin Pediatr 1994; 33: 340-43.
17. Denton A, Davis P. Extreme thrombocytosis in admissions to paediatric intensive care: no requirement for treatment. Arch Dis Child, 2007; 92:515-16.
18. Dame C, Sutor AH. Primary and secondary thrombocytosis in Childhood. Br J Haematol 2005; 129: 165-177.
19. Heng J T, Tan AM. Thrombocytosis in childhood. Singapore Med J 1998;39:485-87.
20. Vora AJ, Lilleyman JS. Secondary thrombocytosis. Arch Dis Child 1993; 68: 88-90.
21. Garoufi A, Voutsioti K, Tsapra H, Karpathios T Zeis PM. Reactive thrombocytosis in children with upper urinary tract infections. Acta Paediat 2001; 90: 448-9.
22. Matsubara K, Fukaya T, Nigami H, Harigaya H, Hirata T, Nozaki H, et al. Age-dependent changes in the incidence and etiology of childhood thrombocytosis. Acta Haematol 2004; 111:132-7.
23. Dame C, Sutor AH. Primary and secondary thrombocytosis in childhood. Br J Haematol 2005;129: 165-77.
24. O'Shea J, Sherlock M, Philip R. Thrombocytosis in childhood. Acta Haematol 2005; 113: 212.
25. Vlacha V, Feketea G. Thrombocytosis in paediatric patients is associated with severe lower respiratory tract inflammation. Arch Med Res 2006; 37: 755-9.
26. Dodig S, Raos M, Kovac K, Nogalo B, Benko B, Glojnaric I, et al. Thrombopoietin and interleukin-6in children with pneumonia-associated thrombocytosis.Arch Med Res 2005; 36: 124-8.
27. Thomas GA, O'Brien RT. Thrombocytosis in children with Hemophilus influenzae meningitis.Clin Pediatr (Phila) 1986; 25: 610-11.
28. Garoufi A, Voutsioti K, Tsapra H, Karpathios T, Zeis PM. Reactive thrombocytosis in children with upper urinary tract infections. Acta Paediatr 2001;90: 448-9.
29. Dharnidharka VR, Kandoth PW. Prevalence of bacteriuria in febrile infants. Indian Pediatr 1993;30: 987-990.
30. Fouzas S, Mantagou L, Skylogianni E, Varvarigou A. Reactive Thrombocytosis in Febrile Young Infants with Serious Bacterial Infection Indian Pediatr. 2010; 47(11):937-43.
31. Dodig S, Raos M, Kovac K, Nogalo B, Benko B, Glojnaric I, et al. Thrombopoietin and interleukin-6in children with pneumonia-associated thrombocytosis.Arch Med Res 2005; 36: 124-8.
32. Thomas GA, O'Brien RT. Thrombocytosis in children with Hemophilus influenzae meningitis.Clin Pediatr (Phila) 1986; 25: 610-11.
33. Garoufi A, Voutsioti K, Tsapra H, Karpathios T, Zeis PM. Reactive thrombocytosis in children with upper urinary tract infections. Acta Paediatr 2001;90: 448-9.
34. Dharnidharka VR, Kandoth PW. Prevalence of bacteriuria in febrile infants. Indian Pediatr 1993;30: 987-990.

35. Fouzas S, Mantagou L, Skylogianni E, Varvarigou A. Reactive Thrombocytosis in Febrile Young Infants with Serious Bacterial Infection Indian Pediatr. 2010; 47(11):937-43.