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Platelets level response after three days therapy in children with acute Immune Thrombocytopenic Purpura (ITP): a 10 years' experience at the tertiary hospital

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ABSTRACT

Background: Immune thrombocytopenic purpura (ITP) is the most common cause of thrombocytopenia in children that characterized by isolated thrombocytopenia that vary in bleeding manifestations. The onset of disease is sudden and a self-limiting condition that requires treatment when clinically significant bleed occurs. A treatment goal is to increase platelet level above safety level and reduce the risk of severe bleeding. This study aims to evaluate the platelets level increment after three days treatment among children with acute ITP.

Methods: An analytic retrospective cross-sectional study was conducted in Haematology-Oncology Paediatric Division Sanglah General Hospital, Bali, Indonesia from October 2008 to October 2018 in ITP patients. Diagnosis of ITP was evaluated based on the clinical manifestation and laboratory finding. Oral corticosteroid medication with dosage 2 mg/kg/day or 4 mg/kg/day with or without platelets transfusion were enrolled in this study from medical records. Data were analyzed using SPSS version 20 for Windows.

Results: There were 93 children met the inclusion criteria and included in this study. A median platelets level at admission was 6.81(1-86.8) x 10^9/L. Majority symptoms of children with ITP in our tertiary care centre presented with mild to moderate clinical bleeding symptoms. Only 5.6% children with platelets level below 10x10^9/L had intracranial bleeding. Median platelets level was 31(2.47-382) x 10^9/l and there was a significant platelets level increment after three days of therapy (P<0.05).

Conclusion: The platelets level increment significantly in children with acute ITP after three days of therapy.

Keywords: immune thrombocytopenic purpura, platelets level, oral steroid, platelets transfusion

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INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an acquired autoimmune haematological disorder often occurs in children that characterized by isolated thrombocytopenia (platelets count <100x10^9/l) an without any systemic diseases.[1,2] Newly diagnosed/acute ITP is thrombocytopenia self-limiting and lasting for 3 months.[3] Childhood ITP affects males and female equally but in infancy more frequent affect females. Peak occurrence is between 2 and 5 years of age. The onset of the disease was sudden with viral illness or immunization few weeks earlier as preceding factor.[4] Previous infection as preceding factor occur in approximately 60% of pediatric ITP.[5] Clinical manifestation involving varies bleeding disorders range from mild (mucocutaneous bleeding) to severe (internal organ bleeding). It is a self-limiting disease and requires treatment only when clinically significant bleeding occurs. Risk of severe and internal bleeding increase up to 3% and 1% respectively.[6] Platelets count less than 10x10^9/L is more likely to cause severe bleeding with only 3% showed significant symptoms as severe epistaxis or gastrointestinal (GI) bleeding.[5]

Treatment varies from drugs until blood transfusion administration. Drug of choice includes corticosteroids, intravenous immunoglobulin (IVIG) and anti-D immunoglobulin with goals of therapy is to increase the platelets count enough to prevent severe bleeding. Management of ITP depends on significant bleeding manifestation with first-line treatment is prednisone 2 mg/kg/day in divided doses orally for 2-4 weeks with tapering after platelets response occurs. Another approach is to use prednisone 4 mg/kg/day for a short period with rapid taper.[2,7] IVIG and anti-D are used if platelets counts < 20x10^9/L and active bleeding.[8]

In Sanglah General Hospital setting, children with acute ITP were treated according to the manifestation of bleeding and platelets level. Initial

treatment started when platelets level < 20x10^9/l with corticosteroid and with or without platelets transfusion depend on manifestation of bleeding. Based on those mentioned above, this study aimed to evaluate the platelets level increment after three days treatment in order to determine the response of therapy during 10 years of study.

METHODS

An analytic retrospective cross-sectional study using secondary data registry was conducted among patients diagnosed with acute ITP on the first admission to the Pediatric Haematology-Oncology ward at Sanglah General Hospital during October 2008-October 2018 period. All of patients included in this study took oral corticosteroid (methylprednisolone or prednisone) with dose 2 mg/kg/day or 4 mg/kg/day with or without platelets transfusion. Subjects who had other chronic types of disease such as systemic lupus erythematosus, viral hepatitis, human immunodeficiency virus, malignancy, bone marrow failure, incomplete data, the treatment not accordance to the standard operating procedure were excluded from the study. The sample size was calculated according to an error rate set at 5% and power 90%, mean difference increment of thrombocyte was 10x10^9/l and total sample was placed at least 65 patients.

Type of ITP was disease severity based on bleeding manifestation that classified into type A (mild), without bleeding manifestation or minor petechiae and bruise without mucosal bleeding; type B (moderate), major petechiae, bruise and involve mucosal bleeding; type C (severe), severe mucocutaneous bleeding with involvement of retina, intracranial or other internal bleeding and life-threatening. Nutritional status defined as Waterlow classification based on actual body weight. Response to therapy divided as "Complete response" (CR) is defined as any platelets count of at least 100x10^9/L, "Response" (R) is defined as any platelets count between 30 and 100x10^9/L and at least doubling of the baseline count. "No response" (NR) is defined as any platelets count lower than 30x10^9/L or less than doubling of the baseline count.[3] All statistical analyses were conducted with SPSS version 20 for Windows. Kolmogorov-Smirnov test to determine the distribution of the data. Wilcoxon, Mann-Whitney, Kruskal Wallis test to compare the platelet difference were used in this study because the data were not normally distributed. P values of < 0.05 were considered statistically significant.

Table 1. Baseline characteristics of respondents based on medical records and platelet counts

Characteristic	N (%)	Median (Min-Max) Platelet (x10^9)
Age		
< 1 years	37 (39.78)	5.24 (1-23.8)
1-10 years	50 (53.76)	7.75 (1-86.8)
> 10 years	6 (6.46)	6.95 (3.8-16.3)
Sex		
Male	54 (58)	6 (1.28-25.78)
Female	39 (42)	7 (1-86.8)
Viral infection		
Yes	37 (39.78)	7.6 (1-28)
No	56 (60.22)	5.92 (1-86.8)
Type of ITP		
A (mild)	40 (43)	8 (1-28)
B (moderate)	42 (45.2)	6.4 (3-86.8)
C (severe)	11 (11.8)	4.99 (2.99-23.8)
Nutritional status		
Normal	63 (67.7)	7.6 (1-86.8)
Malnutrition	16 (17.2)	4.78 (3-28)
Overweight	14 (15.1)	5.75 (2-16.3)
Therapy		
Steroid	50 (53.76)	7.89 (1-86.8)
Steroid + transfusion	43 (46.24)	6 (1.28-23.8)

RESULTS

We reviewed 109 children retrospectively during the study period who diagnosed with acute immune thrombocytopenic purpura (ITP) in 10 years of study. About 12 samples were excluded due to incomplete data and 4 other samples were also excluded due to did not follow the standard operational procedure (SOP) for treatment. The male to female ratio was nearly to equal (1.38:1). The median age at the time of presentation was 2 (0-12) years (Table 1).

Amongst 93 children who enrolled in this study, the median platelets level at admission was 6.81 (1-86.8) x 10^9/L. Seventy-one children (76.3%) initially presented with level platelets below the cutoff of 10x10^9/L. Furthermore, 39.8% children had the history of preceding viral illness whereas the upper respiratory tract infection was the more frequent. Most children (41.93%) with age 1-10 years had initial platelets level below 10x10^9/L. Table 1 showed the demographic and clinical characteristics of the children related to platelets level at admission.

On clinical examination, bleeding manifestation was varied from mild to severe as showed in Table 2 and Table 3. Petechiae, bruises, and mucosal bleeding remained the common bleeding presentation. Other internal bleeding were hematemesis, melena, hematuria and hemoptysis. Ten out (14%) of 71 patients with initial platelets level ≤ 10x10^9/l had internal bleeding as complications and from thus 4 (5.6%) children had intracranial bleeding (Table 2 and 3).

Table 2. Clinical features of bleeding manifestations

Clinical Manifestations	N (%)
Petechiae	82 (88.2)
Bruises	57 (61.3)
Mucosal bleeding	52 (55.9)
Epistaxis	18 (19.4)
Internal bleeding	11 (11.8)

Table 3. Platelets level during admission associated with the bleeding manifestation

Platelets level (x10^9/l)	Bleeding manifestation, n (%)		
	Mild	Moderate	Severe
< 10	25 (34.70)	37 (51.40)	10 (13.89)
11-20	13 (76.50)	4 (23.50)	0 (0.00)
> 20	2 (50.00)	1 (25.00)	1 (25.00)

Table 4. Median platelets level at admission and after 3rddays therapy

Platelet counts	Median (Min-Max) x 10^9/L	P-value
At admission	6.81 (1-86.8)	0.00*
After therapy	31 (2.47-382)	

*Wilcoxon Test: considered statistically significant if P value less than 0.05

Table 5. The characteristics of platelet levels increment

Characteristic		Median (Min-Max)	P-value
Sex	Male	35.2 (-10 – 271.4)	0.065
	Female	19 (-81.6-372.2)	
Viral infection	Yes	22 (-5.3 – 271.4)	0.7
	No	25.38 (-81.6– 372.2)	
Therapy	Steroid	32.5 (-81.56-372.16)	0.52
	Steroid and transfusion	19 (-5.3-271.4)	
Age	< 1 years	20 (-10 – 372.2)	0.39
	>10 years	10.5 (-5.3 – 115)	
	1-10 yearas	28.54 (-81.6-271.4)	
Nutritional status	Malnutrition	18.14 (-1 – 185.12)	0.62
	Overweight	48.5 (-5.3 – 372.2)	
	Normal	22 (-81.56 – 271.4)	
Type of ITP	A	26 (-10-213)	0.37
	B	19 (-81.6 – 372.2)	
	C	4.75 (-5-182)	

After 3rd days of therapy, forty-three children (46.2%) found out as no response, twenty-eight children (30.1%) response and twenty-two children (23.7%) complete response. Response and complete response to the therapy mostly occurred in children aged between 1-10 years old up to 17.2% and 15% respectively. Median platelets level after therapy was 31x10^9/l (range, 2.47-382 x10^9/l). After 3rd days of therapy, 40% children treated with steroid and 53% children treated with combination steroid and transfusion showed no response. Increment platelets showed by mean platelets level difference between at admission and three days after therapy was 58.5 (± 76.58) but not normally distributed (Table 4).

At 3rd days the following therapy, increment of platelets level was evaluated in accordance with baseline characteristic in Table 5. Sex, nutrition status, type of ITP, preceding viral infection, and age at diagnosis were not significant predictors of platelets level increment (Table 5).

DISCUSSION

ITP is clinically bleeding disorder with aetiology remains unclear and several different mechanisms demonstrated as precipitating causes. The diagnosis of ITP in children is essentially an exclusion that should differentiate from other conditions by medical history and physical examination. Medical history includes severity of bleeding, systemic symptoms, history of respiratory infections, recent live viral vaccine, medications and family history of bleeding disorder. Clinical examinations reveal healthy children with bleeding manifestation as platelets level decrease. Two-thirds of children, disease onset often preceded by an infection which mostly upper respiratory tract infection in previous few days to several weeks.[7-10] In this study, diagnosis of acute ITP primarily based on clinical and laboratory finding. Mostly, children age 1-10 years presented with severe thrombocytopenia, which differs from a study conducted in Pakistan with predominantly among children above 10 years.[2] This study obtained 39.8 % children had preceding viral infection and all of them had upper respiratory tract infection, while a study in Pakistan demonstrated the history of upper respiratory tract infection in 12.6%.[2] The setting from previous study in Pakistan was also in the tertiary care centre. The lower prevalence from previous study might be due to poor history taking or people in Pakistan as developing country do not register minor illnesses.[2] There also less frequent occurrence of infection in children < 1 year that might be due to less contact with other children.[11]

There is no clear evidence of a direct correlation between the degree of thrombocytopenia and bleeding symptoms, especially at lower platelet counts.[12] The most severe complications of ITP are intracranial bleeding, predominantly in platelets level <10×10^9/L with estimation at a frequency of 0.19%–0.78%.[13] In this study, majority of children presented clinical bleed symptom as mild to moderate, 5.6% children with platelets count

below $10x10^9$/L had intracranial haemorrhage as bleeding manifestation. A similar result from study in Pakistan reported 89.3%, 78.6% and 1% patients had bruise, petechiae, and intracranial bleeding as initial bleeding manifestation respectively.[2] Another large cohort study also reported that more than half patient had mild to moderate bleed symptom.[14]

The principal for treating children with acute ITP is to increase platelets to safety level and prevent severe bleeding, mainly intracranial bleeding. Corticosteroid is used because its effect by reducing the production of anti-platelets antibodies, decreasing clearance of opsonized platelets and increase vascular stability in ITP.[6] Long-term corticosteroid is associated with significant adverse effect and also do not show durable responses thus often used in the short term only.[15] Recently in children, a shorter course of corticosteroid (2-4 mg/kg per day for 5-7 days) is chosen with spontaneous improvement achieved within days to weeks.[13] Platelets transfusion should be started immediately in significant bleeding manifestation, although may not increase platelets level immediately but instead platelets will be recruited at the site of bleeding and stop the bleeding process. In this study, children got oral corticosteroid (methylprednisolone or prednisone) with dose 2 mg/kg/day or 4 mg/kg/day with or without platelets transfusion. From such children had received combination corticosteroid and transfusion in 46.2% cases and 53.76% children achieved platelets level ≥ $30x10^9$/L. The increment of platelets level at 3rd days of therapy was significant. The previous study by Carcaoet al., in Canada found that 88% of children achieved a platelets level greater than $20x10^9$/L within eight days of starting short-course oral prednisone therapy (4 mg/kg/day) for four days without tapering.[16] This result also quite similar with study by Jayaraman, et al., that found 40% increase of platelets level > $50x10^9$/L in experimental group (prednisolone 5 mg/kg/day for 4 days) compared to control (prednisolone 2 mg/kg/day for 14 days then tapering off followed by stop at day 21st) by day 3 of treatment.[17] However, in our hospital setting select methylprednisolone as the first-line corticosteroid due to having stronger anti-inflammatory properties.

In this study, the increment of platelets level was not influenced by gender, age at diagnosis, nutritional status, preceding viral illness and type of ITP. Gender predominant in ITP had been not described adequately in previous study.[18] A study from Donato et al. had observed difference between three groups of age with age < 1 year showed a high percentage of recovery in acute ITP (89.8%), children between 1-8 years had recovery rate similar as average population (71.3%), whereas almost 50% older children had chronic ITP.[19] Although none of the published studies has declared specifically association between nutritional status and response to therapy in child with ITP, it might due to different treatment dose affected by body weight.

An acute infection often appears to be an initial trigger, but that may only potentiate an already established immunologic disturbance by virus-specific antibodies that cross-react with platelets.[5] Type of ITP based on severity of bleeding manifestation that occurs regardless of platelets level. Although the link between thrombocytopenia and bleeding is well established, there is no clear evidence of a direct correlation between the degree of thrombocytopenia and bleeding symptoms, especially at lower platelet counts. Thus, bleeding in ITP is heterogeneous, unpredictable, and likely based on a composite of other risk factors.[13] However, our data were not able to explain difference in the clinical presentation between each risk factors and increment of platelets level.

CONCLUSION

Majority of patients acute ITP at Paediatric Division Sanglah General Hospital Denpasar had mild to moderate clinical symptom on presentation. The response to the treatment of oral corticosteroid with or without platelets transfusion showed significantly increment of platelets level. It appears that various factors can affect the response of therapy; therefore, further prospective study is needed to explore the influence factors.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding the manuscript

ETHICS CONSIDERATION

Ethics approval has been received from the Ethics Committee, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia prior to the study being conducted.

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AUTHOR CONTRIBUTIONS

Ketut Ariawati is responsible for the conceptual framework, data gathering, and reporting the results of study. I Made Karma Setiyawan is responsible for the preparing draft of manuscript and data analysis.

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