Section: Pediatrics

Original Research Article

CLINICOPATHOLOGICAL FEATURES AND RESPONSE TO VARIOUS TREATMENT MODALITIES IN NEWLY DIAGNOSED CHILDREN WITH IMMUNE THROMBOCYTOPENIC PURPURA: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background: Immune thrombocytopenic purpura (ITP) is a type of purpura associated with isolated low platelet count in the presence of normal bone marrow with absence of any other causes of low platelets. ITP often is a benign condition in most children but it has the potential to be life threatening with a risk of primary intracranial bleeding or soft tissue & mucosal bleeding secondary to trauma. Incidence in child is usually during one to seven years old developing skin bruises, petechiae or mucosal bleeding having no significant lymphadenopathy or organomegaly. Initial management options for newly diagnosed childhood ITP includes under observation, use of intravenous immunoglobulin, steroids, anti-D immunoglobulin alone or in combination. The lack of evidence-based management protocol is a cause for poor management of ITP. This study was undertaken with an objective to assess various clinical presentations of ITP and its management and response to therapy. **Materials and Methods:** The present Prospective observational study was carried out in a tertiary care hospital from 1st October 2019 to 30th September 2021 amongst with suspected ITP admitted / visited department of pediatrics. It included 50 children newly diagnosed with ITP ranging from age group of 6 months to 18 years. **Result:** Average age was around 5 years. Male to female ratio was 2:1.125. Although skin bleed was present in maximum number of cases 40(80%), mucosal bleeds was noted in 16 (32 %) patients. Platelet < 20000 was found in maximum cases i.e. 38 (76 %) before the treatment. Almost all patients were treated with medications. After 6 months follow up, it was noted that maxium children responded to all forms of therapy options 48 (96%). **Conclusion:** ITP is benign disease where much apprehention is created due to low platelet count on machine rather than severity of bleeding manifestations. Majority of patients respond to various treatment modalities. Oral prednisolone for shorter period of time is equally effective than Inj. methylprednisolone which needs hospitalization and costlier IV Immunoglobulin therapy.

INTRODUCTION

Purpura is a condition of red/purple discolored spots on the skin which doesn't blanch on applying pressure. It is caused by bleeding underneath the skin secondary to platelet disorders, vascular disorders, coagulation disorders or any other causes. Immune thrombocytopenic purpura (ITP) is a type of purpura associated with isolated low platelet count in the presence of normal bone marrow with absence of any other causes of low platelets.[1] Complete blood count shows isolated thrombocytopenia with normal Hb, WBC level and normal peripheral smear.

Acute disease often follows an infection which spontaneously resolves within two months. Chronic disease often persists longer than twelve months with an unknown cause. ITP often is a benign condition in most children but it has the potential to be life threatening with a risk of primary intracranial

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bleeding or soft tissue & mucosal bleeding secondary to trauma.

Prevalence of ITP is estimated to be occurrence of 50 to 100 new cases per million per year amongst which children contribute to half the number.[2-4] In adults remission rate is 20 to 40 %.[5] Male to female ratio in children cases is almost equal and in adult cases it ranges between 1:1.2 to 1:1.7. Median age range of incidence of ITP in adults is about between 56 to 60 years.[6]

ITP is an acquired hematological idisorder with the production of auto-antibodies against platelets leading to isolated thrombocytopenia, in the absence of other causes of thrombocytopenia such as drugs, infections, malignancy, or other autoimmune diseases.[7,8] It commonly affects children between one to seven years of age.[9,10] Newly diagnosed ITP usually runs a benign, self-limiting course with or without treatment. Complete remission occurs commonly within 6 to 12 weeks in the majority of children. However, 20 to 30 % of children's will continue to have persistent low platelets count with bleeding symptoms beyond six months.[11]

Clinical features of ITP includes spontaneous formation of bruises and petechiae especially on the extremities, bleeding from the nostrils and/or gums and menorrhagia. These starts appearing when platelet count goes below 20,000 per microliter.[12] Serious and possibly fatal complications include subarachnoid or intracerebral hemorrhage, lower gastrointestinal bleeding or other internal bleeding caused by blunt abdominal trauma in a motor vehicle crash.[13]

Initial management options for newly diagnosed childhood ITP includes under observation, use of intravenous immunoglobulin, steroids, anti-D immunoglobulin alone or in combination.[14,15] Children who develop chronic ITP may benefit from TPO agonists Romiplostim and Eltrombopag, chimeric monoclonal antibody (anti-CD20) Rituximab, splenectomy.[16,17] The lack of evidence-based management protocol is a cause for poor management of ITP.

This study was undertaken with an objective to assess various presentations of ITP, evaluate treatment modalities and response to different therapies.

MATERIALS AND METHODS

The present Prospective observational study was carried out in a tertiary care hospital after the approval of the institutional ethics committee. The study was completed in duration of two years from 1st October 2019 to 30th September 2021. The study was conducted amongst 50 children with suspected ITP admitted / visited department of pediatrics.

Inclusion Criteria

Newly diagnosed cases of ITP in paediatric patients ranging from age group of 6 months to 18 years of age.

Exclusion Criteria

Chronic cases of ITP, Patients not willing for the therapy.

Methodology: All the patients between 6 months to 18 years of age presenting in the paediatric EMS/OPD with ITP (not started treatment) or having clinical features suggestive of ITP like ecchymosis, purpuric patches, bleeding tendencies were enrolled in the study. For confirmation of diagnosis investigations like CBC, and peripheral smear, PT/APTT and bone marrow examination were done. Diagnostic criteria of ITP are thrombocytopenia with normal blood counts and peripheral smear and no clinically apparent condition associated with thrombocytopenia. Investigations like CBC evaluation was done by coulter method Siemens advia 2400, APTT/PT INR – hemosil recomboplastin 24 kit, bone marrow aspiration and trephine biopsy were carried out as per the clinical indication using JAMSHIDI NEEDLE . All the bone marrow aspirate smears were stained with hematoxylin and eosin and examined by same expert in histopathological depatment of our institute.

Patients were started on the following therapies selected on case to case basis according to the physician, a. Tab. Prednisolone 4mg/kg/day for 4 days, b. Inj. IVIG 0.8- 1 gm/kg single dose, c. Inj./Tab. Dexamethasone 10mg/m2/day for 4 days, d. Inj. Methylprednisolone 30 mg/kg/day for 3 days.

Response to above therapies was recorded by noting improvement in clinical response and in platelet count at various time points such as 1 week, 1 month and 6 months. Any side effect/untoward event occurring during therapy were noted.

Statistical Analysis: Data will be entered in Microsoft excel and analysed using SPSS version 24.0th. Mean and SD will be calculated for quantitative variables and proportions for categorical variables. Also data will be represented in form of visual impression like bar diagram etc. Paired t test will be performed for comparison of pre and post test data. P- value of <0.05 will be considered statistically significant.

RESULTS

The data was analysed from the study conducted amongst 50 children with suspected ITP admitted / visited department of pediatrics.

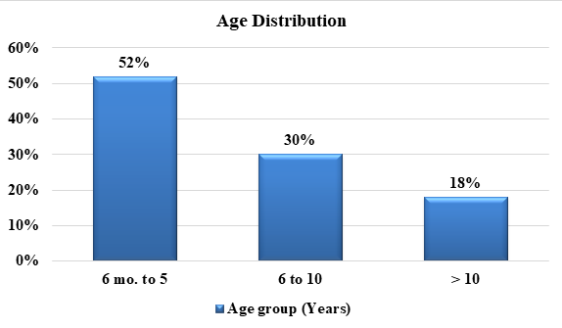

Figure 1: Distribution of Cases according to Age

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[Table 1] Shows distribution of Cases according to Age. Maximum cases i.e. 26 (52 %) were found of age group 6 months to 5 years. This is followed by 15 (30 %) cases between age group 6 to 10 years, 9 (18 %) cases from above 10 years.

[Table 2] shows distribution of Cases according to clinical Signs. Petechiae, Pallor, Ecchymosis and Purpura were the main signs found during examination in ITP patients with prevalence in 40 (80 %), 39 (78 %), 39 (78 %) and 38 (76 %) cases respectively.

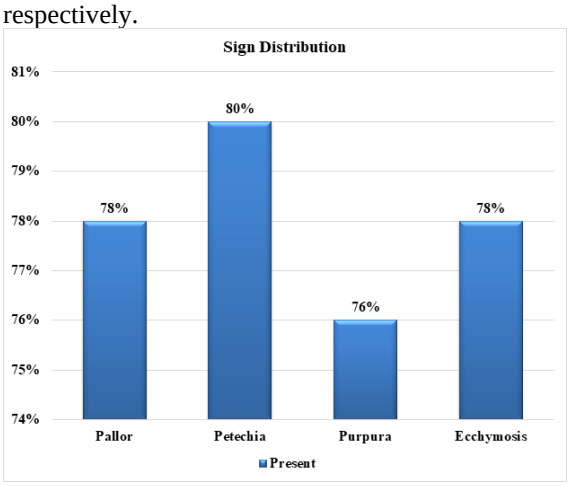

Figure 2: Distribution of Cases according to clinical Signs

[Table 3] Shows distribution of Cases according to the Site of Bleeding. Skin bleed was present in maximum number of cases 40(80%), whereas Mucosal bleed was found in 16 (32%) and Deep Bleed was found in 7 (14%) patients of ITP

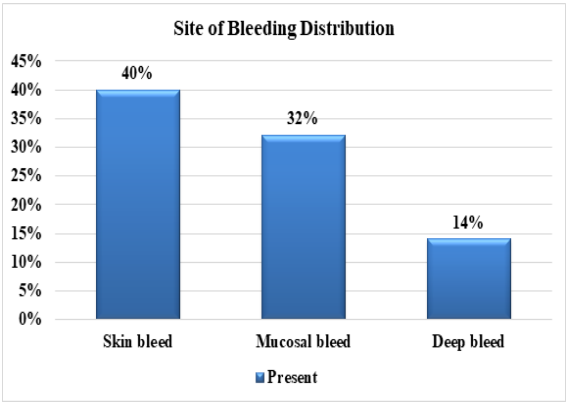

Figure 3: Distribution of Cases according to Site of Bleeding

[Table 4] Shows distribution of Cases according to the Platelet count. Platelet < 20000 was found in maximum cases i.e. 38 (76 %) before the treatment. Platelet count in 20000 to 50000 range was found in 10 (20 %) cases. Platelet count in 51000 to 100000 range was found in 2 (4 %) cases.

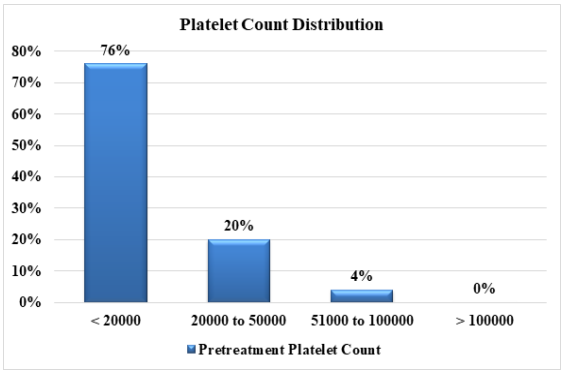

Figure 4: Distribution of Cases according to Haemogram

[Table 5] Shows distribution of cases according to the final outcome response. After 6 months of treatment with Oral Prednisolone positive response was found in 6 (85.71 %) cases total out of 7 cases, with Inj. Methylprednisolone in 30 (100 %) cases total out of 30 cases, with Inj. IVIG in 2 (100 %) cases out of 2 cases, with Inj. Dexamethasone in 10 (90.90 %) cases out of total 11 cases. There was no optimal response at 6 months in 1 case (14.29%) out of 7 cases who received Oral Prednisolone and 1 case (9.10%) out of 11 cases who received Inj Dexamethasone.

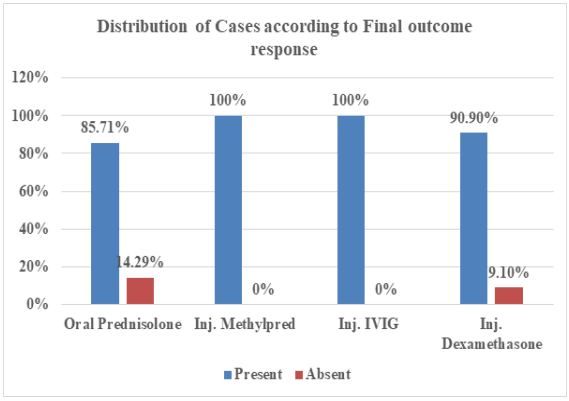

Figure 5: Distribution of Cases according to the Final outcome response

Table 1: Distribution of Cases according to their Age.

Sr. No.	Age group (Years)	Number of Cases (N)	Percentage (%)
1.	6 months to 5	26	52 %
2.	6 to 10	15	30 %
3.	> 10	9	18 %
Total		50	100 %

Table 2: Distribution of Cases according to clinical Signs

Sr. No.	Signs	Present N (%)	Absent N (%)
1	Pallor	39 (78 %)	11 (22 %)
2	Petechiae	40 (80 %)	10 (20 %)
3	Purpura	38 (76 %)	12 (24 %)

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4	Ecchymosis	39 (78 %)	11 (22 %)

Table 3: Distribution of Cases according to the Site of Bleeding

Sr. No.	Site of Bleeding	Present N (%)	Absent N (%)
1	Skin bleed	40(80 %)	10(20 %)
2	Mucosal bleed	16 (32%)	34 (68%)
3	Deep bleed	7 (14%)	43(86%)

Table 4: Distribution of Cases according to the Platelet count

Sr. No.	Platelet count (Lakh/dl)	Number of Cases N	Percentage%
1	< 20000	38	76 %
2	20000 to 50000	10	20 %
3	51000 to 100000	2	4 %
4	> 100000	0	0 %
Total		50	100 %

Table 5: Distribution of Cases according to the Final outcome response (clinical and blood profile response)

Sr. No.	Treatment	After 6 Month Response		Total	P Value
		Present N (%)	Absent N (%)		
1	Oral Prednisolone	06 (85.71 %)	01 (14.29 %)	07 (100 %)	0.261 (P<0.05)
2	Inj. Methylprednisolone	30 (100 %)	00 (00 %)	30 (100 %)	
3	Inj. IVIG	02(100 %)	00 (00 %)	02 (100 %)	
4	Inj. Dexamethasone	10 (90.90 %)	01 (9.10 %)	11 (100 %)	
Total		48 (96 %)	02 (04 %)	50 (100 %)	

DISCUSSION

ITP is a disease which is seen most commonly among the pediatric age group. Most of the patients are confirmed by using PBS and bone marrow examinations and it is important to know its complete clinical and morphological study to further evaluate and start therapy accordingly. To treat newly diagnosed patients of ITP it is decided based on various factors such as prevention of bleeding, increase in the platelet count, cessation of hemorrhagic manifestations and also to induce remission. Currently corticosteroids, IV Ig and Anti D are used as first line drugs which increase the platelet count in most of the patients. The knowledge and the literature based on clinico morphological aspects and treatment modalities of pediatric ITP is less and under research. Hence with this objective the present study was undertaken in 50 newly diagnosed cases of ITP and the results obtained from the present study are summarised below.

In the present study maximum cases i.e. 26 (52 %) were found of age group 6 months to 5 years followed by 15 (30 %) cases between age group 6 to 10 years, 9 (18 %) cases from >10 years. Mean ± SD of age was 5.97 ± 4.14

In the similar study by Ashida Krishnan et al (2020),[18] they analysed 174 cases of ITP. The age of children ranged between 3 months to 15 years of age, 42 % (n = 74) of cases were seen in 1 - 5 years of age, followed by 35 % (n= 62) cases in > 5 to 10 year age range. Children aged more than 10 years constituted 9 % (n = 17) and those less than one year of age constituted 12 % (n = 21).

This concluded that the maximum number of patient in the above conducted study belonged to the age group of 6 months to 5 years (52%) which was comparable to the other studies as well.

In the present study Males were 32 (64 %) and females were 18 (36 %) amongst the total 50 (100 %) cases of ITP. Male to female ratio was 2:1.125

In the similar study by Ashida Krishnan et al (2020),[18] 52 % of children were males (n = 91) and 48 % of children were females (n = 83). Slight male predominance was noted in less than one-year age group and more than 10 years of age

Kuhne et al (2001),[19] in their Intercontinental Childhood ITP study (ICIS) in 2540 paediatric patients found equal sex predilection in all paediatric population with slight male predominance during infancy (M:F = 1.7:1). So the present study states a higher male preponderance compared to female patient ratio which was found similar in the other conducted studies.

In the present study skin bleeds in the form of Petechiae, Ecchymosis and Purpura were the main signs with prevalence 40 (80 %), 39 (78 %) and 38 (76 %) cases respectively. Mucosal bleed was found in 16 (32%) and deep bleed was found in 7 (14%) patients of ITP.

In the similar study by Ashida Krishnan et al (2020),[18] most common clinical presentation noted were petechial rashes in 71 % (n = 124) followed by ecchymosis and oral bleeding. Epistaxis, melaena, subconjunctival haemorrhage, increased menstrual bleed and haematuria were other less common clinical presentations noted. Clinical examination of patients revealed pallor in 7.4 % cases (n = 13), increased body temperature in 13 cases (7.4 %), significant lymphadenopathy in 6.3 % (n = 11) and splenomegaly in 1 % cases (n = 3).

Choi et al,[20] (1967) in their study found common presentation of immune thrombocytopenic purpura were petechiae and purpura (71 %) followed by ecchymosis (13 %). Bleeding from oral cavity, nostrils constituted only minor percentage.

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Bolton-Maggs et al,[21] (1997) also showed similar results with high prevalence of petechiae and purpura in their study with rest of the bleeding manifestations and clinical findings as minor findings.

Blanchette et al,[22] (2008) describes in 5 % to 10 % of children with ITP small cervical lymphadenopathy can occur in young children, and slightly palpable spleen can also be present.

Overall clinical findings in the present study suggest that petechiae (80%), pallor(78%), ecchymosis(78%) and purpura(76%) are the main signs seen with skin bleed(80%)being the most common among the bleeding manifestations which is comparable with the studies studies described above.

In the present study platelet count less than 20,000 was found in maximum cases i.e. 38 (76 %), ranging from 20000 to 50000 was found in 10 (20 %) of the cases, ranging from 51000 to 100000 was found in 2 (4 %) cases whereas no patients found with Platelet count > 100000 before the treatment.

In the similar study by Ashida Krishnan et al,[18] (2020) they assessed platelet count and peripheral smear. Thrombocytopenia was graded as:

a. mild (10,000 – 75,000 cells / mm3),

b. moderate (75,000 – 20,000 cells / mm3) and

c. severe (< 20,000 cells / mm3).

Of which Maximum (74 %, n = 128) children had moderate thrombocytopenia with platelet counts ranging from 26,000 – 50,000 while the severe thrombocytopenia constituted 21 % (n = 36) and mild thrombocytopenia 6 % (n = 10). Isolated thrombocytopenia with normal counts and normal WBC AND RBC was the most common peripheral blood morphology observed in ITP cases studied (67.8 %, n = 118).

In a similar study by Sinan Akbayram et al,[23] (2011) Approximately 75% of patients having mild symptoms at their initial presentation of ITP, included the majority of children with platelet counts less than 10000. The mean initial platelet count in this study was 14200 slightly lower than previous reports that ranged from 15400 to 19000.

So the overall outcome associated with the hematological profile before the start of treatment when compared with different studies and the present studies carries patients belonging to platelet range of less than 20,000 in the present study on a higher side(76%) compared to patients having platelets in range of 20000 to 750000 on a higher side in other studies.

In the present study Oral Prednisolone was given in 7 (14 %) patients. Inj. Methylprednisolone was given in 30 (60 %) patients. Inj. IVIG was given in 2 (4 %) patients. Inj. Dexamethasone was given in 11 (22 %) patients. After 1 week of treatment clinical response was found in 36 (72 %) cases. After 1 month of treatment clinical response was found in 43 (86 %) cases. After 6 month of treatment clinical response was found in 48 (96 %) cases. After 1 week, 1 month and 6 month of treatment blood profile response in the form of platelet count was evaluated. Result was statistically significant (P< 0.00001) which shows there is correlation between two variables i.e. blood profile response and treatment duration. After 1 week of treatment clinical response for different treatment modality were evaluated. In Oral Prednisolone out of 7 patients positive response was found in 6 (85.71 %) cases, with Inj. Methylprednisolone in 24 (80 %) cases out of 30 patients, with Inj. IVIG in 1 (50 %) case out of 2 patients, with Inj. Dexamethasone in 5 (45.46 %) cases out of 11. After 1 month of treatment with Oral Prednisolone positive response was found in 6 (85.71 %) cases, with Inj. Methylprednisolone in 26 (86.67 %) cases, with Inj.IVIG in 2 (100 %) cases, with Inj. Dexamethasone in 9 (81.81 %) cases. After 6 months of treatment with Oral Prednisolone positive response was found in 6 (85.71 %) cases, with Inj. Methylprednisolone in 30 (100%) cases, with Inj. IVIG in 2 (100 %) cases, with Inj. Dexamethasone in 10 (90.90 %) cases. In Oral Prednisolone 1 case (14.29%) out of 7 cases and in Inj. Dexamethasone 1 case (9.10%) out of 11 cases resulted in no response post 6 months follow up in the final outcome.

In the similar study by Ashida Krishnan et al,[18] (2020) analysed platelet count after steroid therapy / IVIG therapy in all cases diagnosed with ITP. Immediate response showing rise in platelet count within 72 hours observed in 147 cases (84 %), whereas 14 % cases (n = 24) showed delayed response to treatment. Treatment response was absent in three children (1.7 %) who were referred for further evaluation.

Watt et al,[2] (2004) reported out of 256 ITP cases treated with steroids, 235 showed good response.

Sinan et al,[23] (2011) conducted study in 260 acute ITP patients; out of 247 people who received therapy 180 patients were treated with high dose steroids, 32 patients with ordinary steroid dose, 20 with IVIG and 11 patients with combination of steroid and IVIG. The response in high dose steroid was 80 % (n = 145), ordinary steroid was 78 % (n = 25), IVIG was 80 % (n = 16) and for combination therapy was 82 % (n = 9).

George et al,[24] (1996) reported 58.3 % cases of paediatric ITP in his study had delayed response to therapy with complete response only at six month period and 6.6 % cases had no response to therapy at all. The treatment response of the cases by grading platelet count into non severe and severe grade showed by chi-square test showed no significant correlation (p value > 0.05).

CONCLUSION

ITP is a benign disease where much apprehention is created due to low platelet count on machine rather than severity of bleeding manifestations.Despite very low platelet counts majority of these children have minor bleeding manifestation and most of them respond to various treatment modalities. Although response to oral Prednisolone can be slower, oral prednisolone for shorter period of time is equally effective when compared to Inj methylprednisolone

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which needs hospitalization and costlier IV Immunoglobulin therapy.

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