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Clinical Profile and Outcome of Patients Presenting with Severe Thrombocytopenia in A Tertiary Care Hospital

Dr Jyoti Jindal[1], Dr Arvind Goyal[2*]; Dr Vikas Garg[3]

[1] Assistant Professor Medicine, Dayanand Medical College & Hospital, Ludhiana
[2] Associate Professor Urology, Dayanand Medical College & Hospital, Ludhiana
[3] Professor Medicine, Dayanand Medical College & Hospital, Ludhiana.

ABSTRACT

BACKGROUND: Thrombocytopenia is a prevalent problem for physicians of many specialties in tropical areas such as India. In many etiological disorders, thrombocytopenia manifests as an asymptomatic condition that might progress to a life-threatening condition requiring blood transfusion. Malaria and dengue fever infections are generally linked with thrombocytopenia, with variable clinical patterns. The most prevalent cause of thrombocytopenia is infection. The aim of present study the clinical profile and outcome of patients presenting with severe thrombocytopenia.
METHODOLOGY: A prospective study was conducted in patients presented with severe thrombocytopenia in Dayanand Medical College and Hospital, Ludhiana from 1/03/2021 to 28/02/2022.The patients were followed up during their hospital stay and further followed up on OPD basis for 6 weeks or till the response was achieved..
RESULTS: Tropical fever was the most common cause of severe thrombocytopenia with 61 cases followed by sepsis with 23 cases. Bleeding manifestations were seen in 43.08% patients. Complete response was seen in 80% of the tropical fever, 43% of sepsis and 66% of ITP patients. Mortality was maximum in patients with sepsis induced thrombocytopenia.
CONCLUSION: Tropical fever is the commonest diagnosis made in patients who are detected to have severe thrombocytopenia. Treatment of the patients varied with the underlying etiology. Mortality was maximum in sepsis induced thrombocytopenia.

Key Words: *Thrombocytopenia, tropical fever, ITP-Idiopathic thrombocytopenic purpura, sepsis, Bleeding manifestations*

***Corresponding Author**
Dr Arvind Goyal
Associate Professor Urology, Dayanand Medical College & Hospital, Ludhiana

INTRODUCTION

Thrombocytopenia can result from the decreased production, increased destruction, increased sequestration of platelets in spleen or combination of these factors. Pseudo thrombocytopenia is the agglutination of platelets in the blood stream leading to false low counts in automated cell counters. It can be ruled out by peripheral film examination. Severe thrombocytopenia is a prognostic risk factor which is associated with increased morbidity and mortality. [1]

Patients with viral, bacterial, fungal and parasitic infection can have thrombocytopenia. Commonly Dengue, Scrub Typhus, Malaria, Rickettsial infections, Meningococci, Typhoid, Leptospira, miliary Tuberculosis, HIV and certain viral infections can cause thrombocytopenia. Clinical presentation of thrombocytopenia varies from being asymptomatic to presenting with bleeding episodes.

This study attempts to determine the common etiologies responsible for severe thrombocytopenia among patients admitted in Dayanand Medical College and hospital and their clinical profile with relevance to bleeding manifestation, requirement of platelet transfusion, steroids and overall impact on the mortality of the patients..

MATERIAL AND METHODS

A prospective study was conducted in patients presenting with severe thrombocytopenia in Medicine and allied specialities OPDs and admitted at Dayanand Medical College and hospital, Ludhiana from 1/03/2021 to 28/02/2022. The patients were followed up prospectively during their hospital stay and further followed up on OPD basis for 6 weeks or till the response was achieved.

Patients were investigated for the cause of severe thrombocytopenia and analyzed based on the need for platelet transfusion/steroids, severity of thrombocytopenia, development of bleeding manifestations, duration of hospital stay and the final outcome of hospital admission. The response of intervention was measured in terms of complete response,

partial response and no response. Response was defined as platelet count more than or equal to $30X10^9$/L and at least 2 fold increase in the baseline value and absence of bleeding.

Complete response was defined as platelet count more than or equal to $100x10^9$/L and absence of bleeding and no response was defined as platelet count less than $30x10^9$/L or less than 2-fold increase of baseline platelet count or bleeding. [2]

Inclusion Criterion:

1) Patient with severe thrombocytopenia (less than $20x10^9$/L)
2) Patient age more than or equal to 18 years

Exclusion Criterion:

1) Patients with mild and moderate thrombocytopenia
2) Patients not willing to take part in the study
3) Age less than 18 years.
4) Patients diagnosed with any malignancy

RESULTS

A total of 123 patients who satisfied the inclusion criteria and were included in the study. Out of a total of 123 patients, 7 patients were lost were lost to follow upof the response to treatment, so the response to treatment was recorded in 116 patients.

Maximum patients presented with severe thrombocytopenia belonged to the age group of 19 – 30 years (24.4%) followed by 31 – 40 years(22%). Majority were males (60.2%) as compared to females (39.8%).9.8 % patients were found to have alcohol history while 90.2% has no alcohol history. There were 80 patients (65%) presenting with severe thrombocytopenia who were associated with the co morbid conditions. Most common was type 2 Diabetes Mellitus (24.4%) followed by Hypertension (19.5%).

Half of the patients presented with severe thrombocytopenia were diagnosed with tropical fever (49.59%) followed by sepsis (18.7%). ITP was found to be the 3rd most common cause (14.63%) of severe thrombocytopenia.

Other causes found in this study included autoimmune (2.44%), tuberculosis (2.44%), drug induced (0.81%) andmegaloblastic anaemia (1.63%). 12 patients (9.76%) were found to have multiple etiologies causing severe thrombocytopenia.

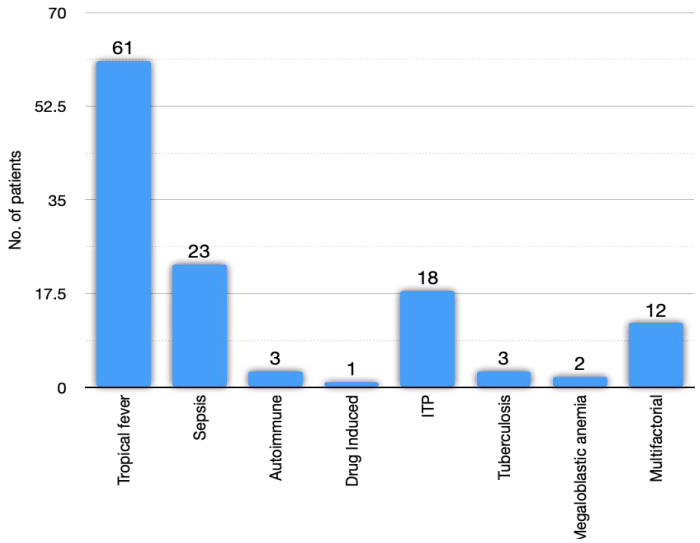

Figure 1: Bar graph showing distribution of etiology of patients presenting to the hospital with severe thrombocytopenia

There were 61 patients who had severe thrombocytopenia as a result of tropical fever. Dengue fever was most common cause of tropical fever (73.77%). The next most common cause (8.20%) was discovered to be dual infections.

Tropical fever was identified in 6 patients (9.84%) in conjunction with various aetiologies. The most common cause of Sepsis in our patients (39.12%) was genitourinary infections. A third of the patients (34.78%) experienced Sepsis as a result of gastrointestinal illnesses. The most common presenting complaint (73.2%) was fever.

In 44 individuals (35.8%), there was generalised body weakness. There were 28 (22.8%) patients who complained of stomach pain. 53 individuals (43.08%) experienced bleeding. In the ITP and Multifactorial groups, almost three-fourths

of the total patients had bleeding symptoms. All patients with Autoimmune and Drug-Induced Thrombocytopenia had some sort of bleeding. In the sepsis group, less than half of the patients (43.47%) displayed these characteristics, whereas one-fourth of the Tropical fever patients displayed bleeding signs. There was no evidence of bleeding in patients with Tuberculosis and Megaloblastic Anaemia.

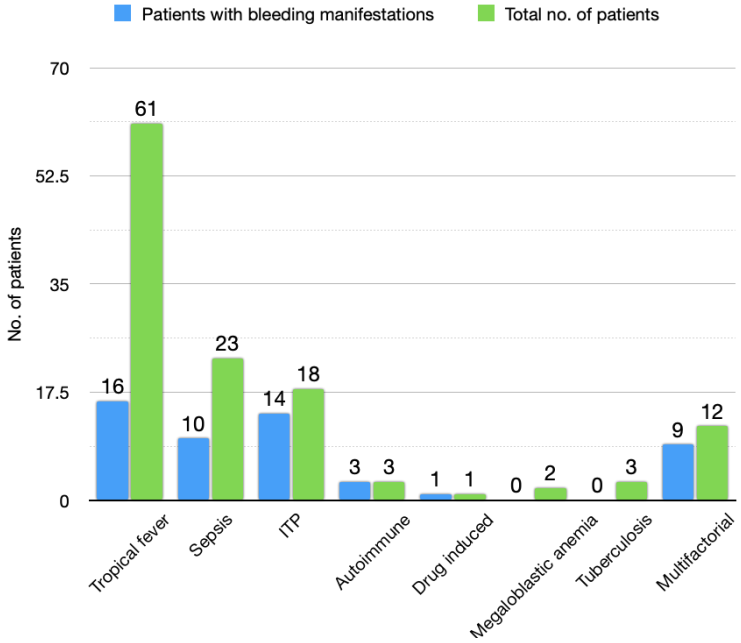

Figure 2: Bar graph showing presence of various bleeding manifestations in different etiologies of thrombocytopenia

Ecchymosis (17.07%) was the most common type of bleeding manifestation, followed by gum bleeding (13.11%), and malena (13.11%). Menorrhagia (4.88%), epistaxis (4.07%), hematuria (4.07%), and subconjunctival haemorrhage (2.44%) were the other types of bleeding manifestations.

In tropical fever, 16 of the 61 individuals developed bleeding symptoms. Malena was the most prevalent bleeding manifestation in tropical fever (9.84%), followed by gum bleeding (8.20%).

In sepsis, 10 of 23 individuals experienced bleeding. Ecchymosis was the most prevalent bleeding manifestation reported in sepsis (26.09%). Gum bleeding was the most prevalent type of bleeding observed (38.89%). All three patients with severe thrombocytopenia due to autoimmune reasons experienced bleeding events such as Malena, menorrhagia, ecchymosis, and hematuria. Hepatomegaly and splenomegaly were observed in 9 (7.3%) and 17 (13.8%) individuals, respectively.

There were 40 patients in whom bone marrow examination was done. Out of them, 25 (62.50%) bone marrow suggested hyper-destructive thrombocytopenia, 4 patients (10.00%)showed Hemophagocytosis in bone marrow and 5 patients haderythroid prominence (12.5%) in bone marrow. Granulomatous inflammation was seen in 2 patients (5.00%) in marrow. Bone marrow examination was done in all the ITP patients, 94.44% of them showed hyper destructive thrombocytopenia and 5.55% showed hyper destructive thrombocytopenia with iron deficiency Anaemia.

Autoimmune work up was done in 37 patients and was negative in 20patients (54.1%). Out of the 17 patients with positive results, ANA-IF 3+and 4+ results were seen in 5 patients (13.5%) and 2 patients (5.4%)respectively. There were total 17 patients with positive ANA IF.

Out of these 17patients, 10 patients had negative ANA profile .4 patients had positive SSA/Ro52 antibody (seen in Sjogren syndrome). Other antibodies seen in the patients included Ku/uctd (seen in undifferentiated connective tissue disorder), DsDNA (seen in SLE) and Lupus anticoagulant (seen in APLA syndrome).

Treatment Response

Blood products were transfused in 81.3% of the patients (100 patients). Steroids were given in 38 patients (30.89%). Thrombopoietin Receptor Agonists (TPO-RA) were received by 3.25% patients (4 patients). Only 2.44% patients were given IVIG.

All of the patients with Thrombocytopenia due to Tropical fever were given only symptomatic treatment. Majority of the patients (80.32%)showed complete response. None of the patients showed No response. Out of a total of 23 patients with Thrombocytopenia due to Sepsis, 4were lost to follow up. Out of these 19 patients, 6 (31.57%) were given steroids. Half of these 6 patients showed complete response, whereas the other half showed no response.12 patients

(63.15%) were given only symptomatic treatment. Half of these patients showed complete response, whereas only 2 showed no response. Only 1 patient was given a combination therapy of Steroid, TPO-RA and IVIG and that patient showed complete response.

16 patients (88.89%) with ITP received treatment with steroids only. 11 of these 16 (68.75%) showed complete response to this treatment and only one patient showed no response. Among the 12 patients who showed complete response to treatment of Thrombocytopenia due to ITP, 11 were given steroids and 1 was given a combination therapy with steroids, TPO-RA agents and IVIG.

Total 41 patients received steroids in our study. Each Dexamethasone and methyl prednisolone were given to approximately one third of the patients receiving steroids. 6 patients were given hydrocortisone. Hydrocortisone was not used as a part of pulse therapy it was given for the patients with refractory septic shock. 5 patients received Prednisolone in our study.4 patients were given Thrombopoietin Receptor Agonists. 2 types of TPO RA were used which includes Eltromobopag and Romiplostim. 3patients received romiplostim and only 1 patient received Eltromobopag in our study. 7 patients out of a total of 123 were lost to follow up and were not in cluded in the analysis of response to various treatment modilities. Approximately two thirds of the patients available for follow up showed complete response.

Response (platelet counts of more than $30x10^9$/L) to treatment was shown earliest in patients with severe Thrombocytopenia due to Tuberculosis and Drug induced Thrombocytopenia. In Autoimmune Thrombocytopenia, response to treatment took an average of 7 days.

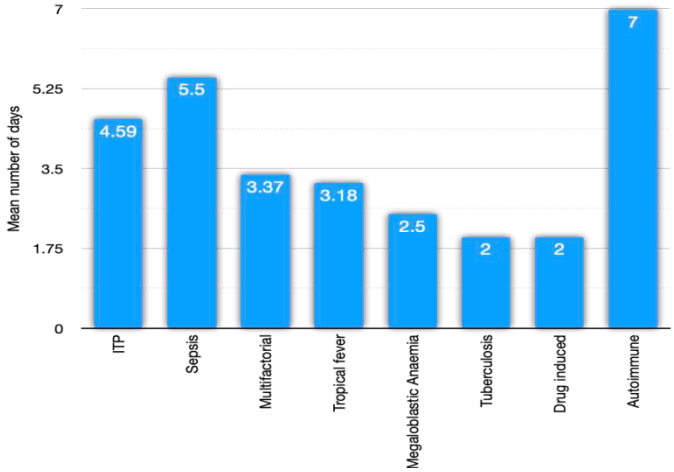

Figure 3: Bar graph showing mean number of days in which response was seen in various etiologies.

Out of a total of 123 patients, 86 (69.9%) did not require ICU care.

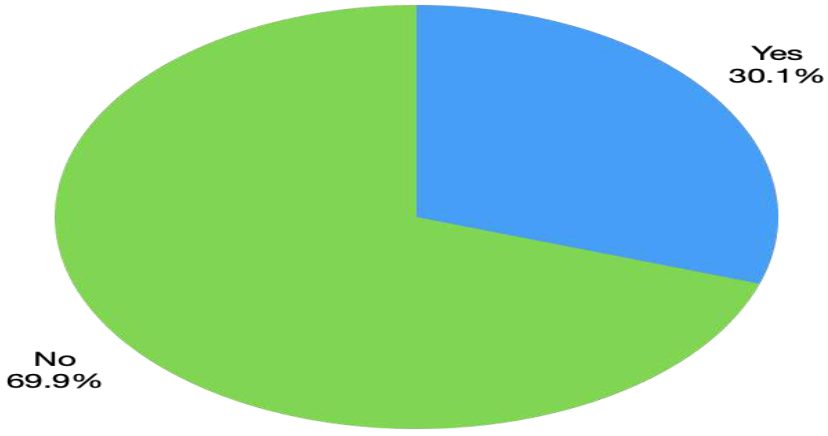

Figure 4: Pie chart showing distribution of patients with severe thrombocytopenia who needed ICU care

Among 116 patients, mortality was seen in only 5 patients (4.31%). Among these 5 patients, 3 patients (60%) were having Sepsis and only1 of them showed partial response to treatment for thrombocytopenia.

Mortality was seen in one patient each due to tropical fever (Dengue shock syndrome with ischemic Hepatitis) and multifactorial causes (Autoimmune cause in combination with respiratory sepsis). All patients with mortality were given

extensive ICU care. Rest of the 111 were either discharged in stable condition (n=99, 85.34%) or discharged against medical advice for various reasons (n=12, 10.34%).

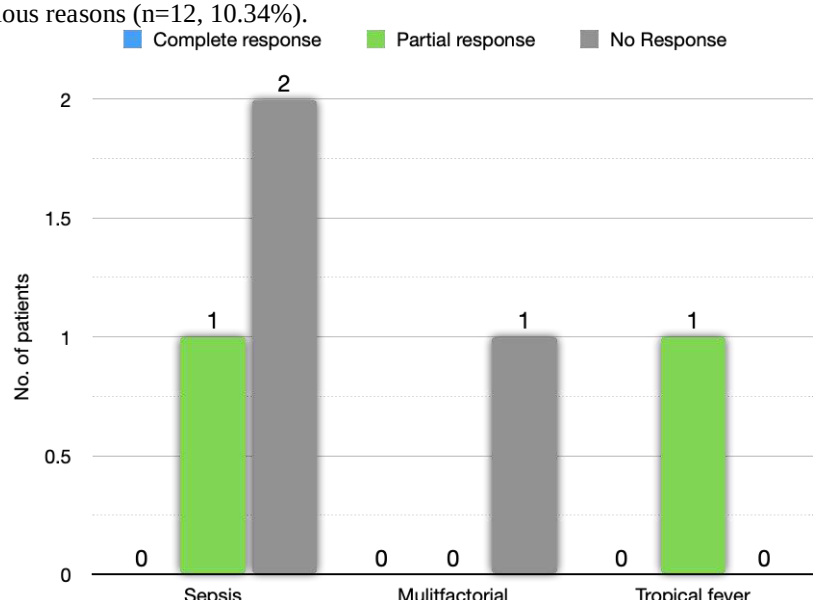

Figure 5: Bar graph showing distribution of patients with mortality with thrombocytopenia due to various etiologies according to the response to the treatment of thrombocytopenia

DISCUSSION

Diagnosis of Thrombocytopenia in itself is a challenge and management is primarily based on the cause of Thrombocytopenia. A total of 123 patients with severe thrombocytopenia were enrolled. Most common etiology of severe thrombocytopenia in our study was Tropical fever (most common-dengue fever) which was seen in almost half of the cases, followed by Sepsis, seen in almost one-fourth of cases. The third most common cause was found to be Immune Thrombocytopenic Purpura (14.63%).Similar to our study, Sridhar et al [3] and Gamit et al [4] found Dengue fever as the most common cause of thrombocytopenia.

In contrast, Lakshmikumar et al [5], and Zhang et al [6] concluded Septicemia followed by Dengue fever as the most common causes. Genitourinary sepsis was most common cause of severe Thrombocytopenia in our study followed by gastrointestinal sepsis. Respiratory sepsis was seen as a cause of severe Thrombocytopeniain 3 patients in our study. Most of the patients with sepsis induced thrombocytopenia in study by Sridhar et al [3] were diagnosed with pneumonia as the primary cause of sepsis (46.5%).

There were 18 patients (14.63%) with severe thrombocytopenia diagnosed with primary Immune Thrombocytopenic Purpura. There were 6 patients in multifactorial etiologies who were diagnosed with secondary ITP. ITP in multifactorial etiology was seen secondary to Tropical fever, Autoimmune etiology and both. In a study by Palau et al [8], secondary ITP was diagnosed in 51 of the total 484 ITP patients, most commonly associated with SLE (n=9,17.6%) and Lymph proliferative disorders. There were 7 patients in our study with Autoimmune component as a cause of Thrombocytopenia. Almost half of them (n=3) had autoimmunity as the only cause of severe Thrombocytopenia whereas in rest of the patients, autoimmunity was associated with other etiologies like Sepsis, Tropical fever and Hemophagocytosis.

In our study one patient was found to have Drug induced severe thrombocytopenia with Methotrexate. Patient had previous history of Rheumatoid Arthritis for which she was taking Methotrexate for 2months prior to presentation to our hospital. In a study done by Lalevee et al [9], 433 cases of cytopenia associated with methotrexate were analyzed. They found that, 19.4% were due tomedication errors, 39% patient were exposed to only methotrexate and41.6% patients were exposed to methotrexate and other drugs. There were 3 patients with severe thrombocytopenia due to Tuberculosis. The diagnosis of Tuberculosis in two patients was madeon basis of Bone marrow findings suggestive of granulomatous inflammation. In a retrospective study done by Hakawi et al [10], out of 394 patients diagnosed with extra pulmonary tuberculosis, 22 patients (5.9%) were identified as having tuberculosis of the bone marrow. Thrombocytopenia was seen in 45% of the patients. Two patients had severe thrombocytopenia due to Megaloblastic Anaemia. One of them had pancytopenia and the other one hadbicytopenia. In a study by Huang et al [11], 1553 patients with Megaloblastic anaemia were studied, thrombocytopenia was seen in 12% of the cases and pancytopenia was seen in 39.3%.

The most common symptom seen in the patient with severe thrombocytopenia in our study was fever which was seen in three fourths of the total patients. Malaise/fatigue/generalized body weakness was seen in almost one third of the total patients. Similarly, in the studies by Lakshmikumar et al [5] and Vimal et al [12], fever was the predominant symptom seen in all the patients with thrombocytopenia. Most common clinical feature seen in patients with Tropical fever in ourstudy was fever followed by generalized malaise. Khan et al [13] and Choudhary et al [14] found most common

symptom in Dengue was fever followed by malaise. Bleeding manifestations were seen in less than half (43.08%) of the patients. Ecchymosis was seen in maximum number of patients (19.51%) followed by Malena (17.07%), Gum bleed (17.07 %), Menorrhagia (6.50%) and Hematuria (5.69%). No incidence of anymajor bleeding event was observed in any patient in our study. In the study of Lakshmikumar et al [5], 43.7% of total patients had bleeding events. Most common event was venipuncture bleed followed by gum bleed. In the study of Sridhar et al [3], 23% of the cases had some sort of bleeding event. Malena was the most common bleeding manifestation observed. In the Immune Thrombocytopenic Purpura group, three fourths of the patients in our study had bleeding manifestations. Most common was Gum bleeding (38.89%) followed by Ecchymosis (27.78%).In the study by Hato et al [15], most common bleeding manifestation in ITP was Purpura (64.80%) followed by Oral mucosal bleed (20.27%).

Management of patients with severe thrombocytopenia depends on the underlying disease. Different treatment modalities used in our study were symptomatic management including transfusion of RDP and/or SDPs and various drugs like Steroids, Thrombopoietin Receptor Agonists (TPO-RA) and IVIG. Almost 80% of the total patients (n=100) in our study received Platelet Transfusions in the form of SDP, RDP or both as per the recommendation that platelets can be transfused prophylactically in patients with severe thrombocytopenia.[16]In study of Sridhar et al[3], one fourth of the total patients (n=26)received platelet transfusion, out of which 23 patients were given transfusion therapeutically and 3 were given prophylactically.

Patients with severe thrombocytopenia due to Tropical Fever were managed symptomatically. Almost 90% of the patients received platelet transfusions. None of the patients received any drugs for thrombocytopenia including steroids, IVIG or TPO-RA in our study. After management with symptomatic treatment including transfusions, complete response was seen in 49 patients out of 61 (80.32%) and partial response was seen in 12 patients (19.67%). There was no patient with severe thrombocytopenia due to tropical fever showing no response. In a study done by Furtado et al [17], platelet transfusions were given prophylactically to all the patients with severe thrombocytopenia due to Dengue fever (n=6). None of the patient in their study received steroidor IVIG. In conclusion, thrombocytopenia due to Tropical fever is usually self-limiting and platelet counts can be improved with transfusions, if required.

In patients with severe thrombocytopenia due to Sepsis, we found that the management of sepsis including the use of appropriate antibiotics and removing the source of the infection plays a major role in the treatment of thrombocytopenia. Out of the total of 23 patients, four patients were lost to follow up, thus response was analyzed in the remaining 19 patients. More than 80%patients with sepsis received platelet transfusions in our study. Steroids were given in only 6 patients, half of them showed complete response and the other half showed no response. There were 12 patients in whom none of the thrombocytopenia specific drugs including steroids, IVIG or TPO-RA were given, among them half of the patients showed complete response, one third had partial response and only 2 patients had no response. There were 16 patients with ITP in whom steroids were given alone, more than two thirds of them showed complete response (68.75%), less than one third showed partial response (25%) and only one patient had no response (6.25%).Chang et al [19] studied the response of steroids in ITP patients and complete response was seen in two third patients (65.2%), partial response in less than one third (23.3%) and no response was seen in11.4%.In our study, high dose Methylprednisolone was used initially followed by maintenance with conventional dose Prednisolone in one third of the total patients with ITP (n=18). All these patient achieved complete response and were discharged in stable condition. In a study by Alpdogan et al [20], it was observed that high dose Methylprednisolone (30 mg/kg/day) is superior to conventional doses of Prednisolone as first line treatment.

Steroids were given to all three patients who had severe thrombocytopenia due to autoimmune reasons, and all three patients responded. Two-thirds of the patients responded completely, whereas one-third responded partially. Platelet transfusions were given to all of the patients in this group.

Out of 116 patients that were available for outcome analysis, mortality was seen in only 5 patients (4.31%). Among these 5 patients, 3patients (60%) had Sepsis induced thrombocytopenia. Mortality rate in the studies of Yadav et al [27] and Furtado et al [17] were19.84% and 2.7% respectively.

CONCLUSION

Severe thrombocytopenia can have varied presentation which can range from patient being asymptomatic to severe life-threatening bleeding events. The basic therapeutic strategy is to diagnose the aetiology of thrombocytopenia and manage the patient along the lines of the underlying aetiology. Prophylactic platelet transfusions can be administered to patients with severe thrombocytopenia. Steroids are the predominant medications in both primary and secondary ITP. In refractory cases, TPO-RA agents and IVIG are helpful adjuncts to steroids.

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