Study of Initial Response of Dexamethasone Therapy to Primary Immune Thrombocytopenia in Tertiary Care Hospital of Nepal

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ABSTRACT

Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, defined as a platelet count less than 100,000/mm3 and the absence of any obvious initiating and/or underlying cause for thrombocytopenia. The current first-line choice of treatment of ITP in adults is steroids and high-dose dexamethasone is considered as an effective and well-tolerated treatment with variable initial response. So this study was conducted to find out initial treatment response of high dose dexamethasone in adults with ITP.

METHODOLOGY: This study was a prospective; hospital based observational study carried out in medicine department of Bir Hospital. Newly diagnosed consecutive ITP patients with platelet count less than 20,000/mm3 or less than 50,000/mm3 with clinically significant bleeding were enrolled in the study. Intravenous dexamethasone at a dose of 40 mg per day for four consecutive days was the initial treatment. Response was evaluated as complete response (CR), partial response (PR), and non response (NR) at day 4 and 10 after the initiation of therapy. Data were compared with the use of Wilcox on test, descriptive statistics, diagrams, chi square (exact) test. Differences were considered to be significant at the level of $P<0.05$.

RESULTS: There were 35 consecutive new patients of ITP admitted in the medical ward with male to female ratio of 1: 1.2 and mean age of 33.2 ± 14.8 years. Twenty nine patients were eligible for therapy. The mean platelet count before treatment was $21,696 \pm 12,394$/mm3. A good initial response to high dose dexamethasone occurred in 24 of the 29 patients (83%). By day 4, the mean platelet count was increased to 58306 ± 49306/mm3 ($P = <0.001$). By day 10, complete response was seen in 8 patients (28%) and partial response was seen in 16 patients (55%). The mean platelet count was 97034 ± 55942/mm3. There were no significant difference seen in mean platelet count at day 10 with the mean platelet count at day 4 ($P=0.22$) and in response among male and female patients 80% and 85% respectively ($P=0.68$). The treatment was well tolerated. Only 14% patients complained minor symptoms.

KEYWORDS: Complete response, immune thrombocytopenia, initial response, partial response, pulse high dose dexamethasone.

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INTRODUCTION

Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, defined as a platelet count less than 100×109/L, and the absence of any obvious initiating and/or underlying cause for thrombocytopenia. It can be classified by duration into newly diagnosed, persistent (3-12 months) and chronic (over a year). Refractory ITP refers to persistent thrombocytopenia despite treatment with steroids or splenectomy. The

incidence of adult ITP varies from 1.6 to 3.3 per 100,000 per year, with slightly higher prevalence in females.[3,4] Not all clinical series of ITP patients had reported difference in race or ethnicity but African Americans seem to be underrepresented.[5] There are limited data on ITP in Nepal. The pathogenic mechanism of thrombocytopenia in ITP is interpreted as increased platelet destruction mediated by auto antibodies and associated complex mechanism involving both impaired platelet production and T-cell-mediated effects.[6] The destruction of platelets leads to an increased production of more effective young platelets in controlling hemostasis resulting milder bleeding manifestations in patients with ITP compared to thrombocytopenia of other etiologies.[7] The clinical presentation in ITP ranges from acute to insidious and minimal to severe bleeding. Only about 40% of patients with platelet counts less than 10,000 per micro liter develop major bleeding. The rate of fatal hemorrhage in untreated ITP is estimated to be less than 5%.[8]

The diagnostic hallmark of ITP is a low platelet counts without identification of alternative causes of thrombocytopenia by history, physical and laboratory evaluations. Tests which are not routinely done in Nepal, are assays for anti platelet antibodies, platelet associated immunoglobulin G and assays for platelet antigen-specific antibodies with variable sensitivity and specificity.[9] Prednisone is most commonly used as a first line therapy of ITP.[10] Debilitating side effects are common when long-term corticosteroid therapy is required to maintain the platelet counts.[11] The results of short courses of high-dose dexamethasone are very promising with different rates of responses 83% to 100%.[12,13,14] Most of the studies were from western population and response rate has not been consistently demonstrated. Therefore, this study was carried out with the objective of determining initial response of pulse high dose dexamethasone used in Nepalese adult patients with ITP.

METHODOLOGY

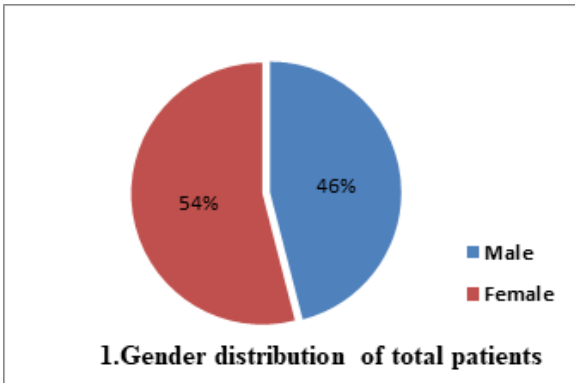
It was a prospective observational study of consecutive new patients of ITP admitted in medicine department in Bir hospital from December 2010 to November 2011. The inclusion criteria were new cases of ITP treated with pulse high dose dexamethasone as initial therapy and platelet count less than 20,000/mm3 or platelet count less than 50,000/mm3 with clinically significant bleeding. Exclusion criteria were patients not willing to give consent, uncontrolled hypertension, diabetes mellitus, active infection, pregnancy, altered renal and liver function and patient known to have secondary thrombocytopenia, ANA, RA positive, and taking drugs causing thrombocytopenia. Patients bleeding symptoms were evaluated using WHO bleeding grades for objective measurement.[15] The treatment protocol was dexamethasone 40mg IV single daily dose for four consecutive days for 4-6 cycles in every 2-4 weeks interval. However in this study, initial cycle of high dose dexamethasone was taken into consideration. Criteria for treatment response were defined as follows: Complete Response (CR):- a rise of platelet counts to normal counts (i.e., more than 100,000/mm3); Partial Response (PR): a rise of platelets to counts between 30,000 and 100000/mm3 or at least double of the base line platelet counts. No response: - when there was no rise in base line platelet count or more than 30,000/mm3 during treatment. Reports of complete blood counts (CBC), random blood sugar and blood pressure measurement were taken before the commencement of pulse high dose dexamethasone therapy, at days 4 and 10. Data were taken from in-patient record files of medical wards, medical record section and medical out-patient department of Bir hospital. The group of patients with treatment response at day 4 was compared with respect to the platelet counts before treatment and 10th day platelet counts. Collected data was analyzed using SPSS 13, 17 program and Microsoft Excel Software. Data were compared with the use of descriptive statistics, diagrams, Wilcox on rank sum test, chi square (exact) test. Differences were considered to be significant at the level of $P<0.05$. All other values were means $\pm$SD unless otherwise indicated.

RESULTS

During the study period of one year, a total of 35 consecutive new patients of primary (idiopathic) immune thrombocytopenia were admitted in the hospital. Among them, 29 patients fulfilled inclusion criteria and were included in the study.

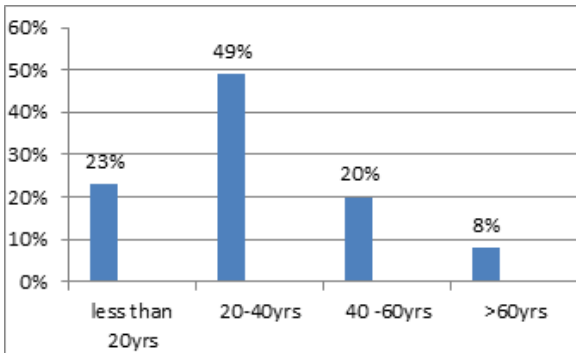
1. Baseline characteristics:-

A) Gender distribution: Of 35 patients, 19 patients (54%) were female and 16 (46%) were male. The male to female ratio was 1:1.2. Six patients did not get pulse high dose dexamethasone therapy and were excluded from the study.

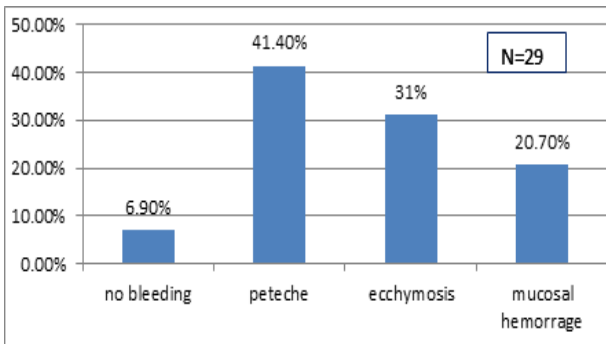


1.Gender distribution of total patients

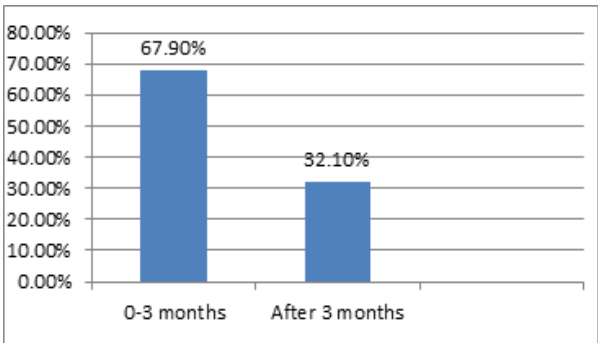
B) Age distribution: The mean age of the patients was 33.2 years with a standard deviation of 14.8 years.



C) Bleeding Symptoms: Among the 29 study patients, 27(93.1%) patients presented with some degree of bleeding symptoms but 2 (6.9%) patients did not have any bleeding symptoms. Minor bleeding symptom and petechiae (41.4%) were the most common symptoms. Clinically significant bleeding symptoms, ecchymosis and mucosal hemorrhage were seen in 15 (51.7%) patients.

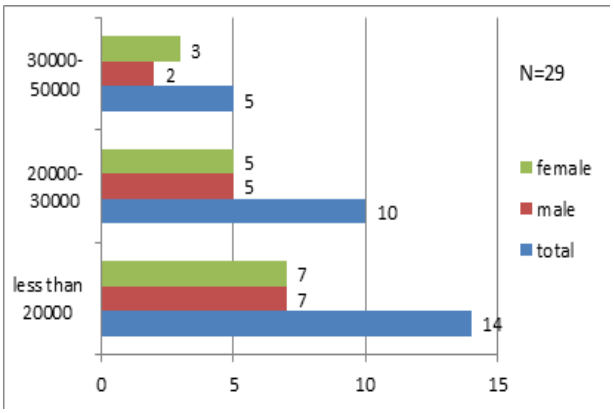


D) Duration of symptoms: Among the symptomatic 27 patients, most of the patients (67.9%) presented with bleeding symptoms within 3 months whereas 32.1% patients after 3 months.

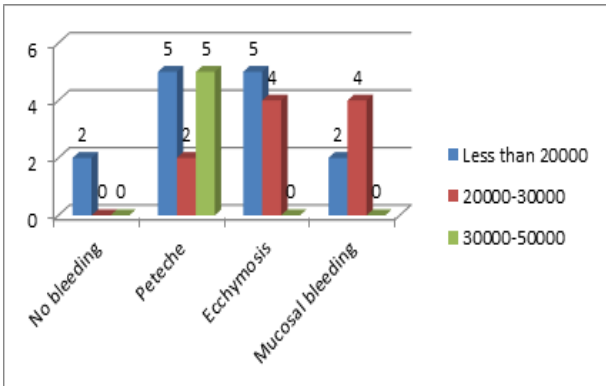


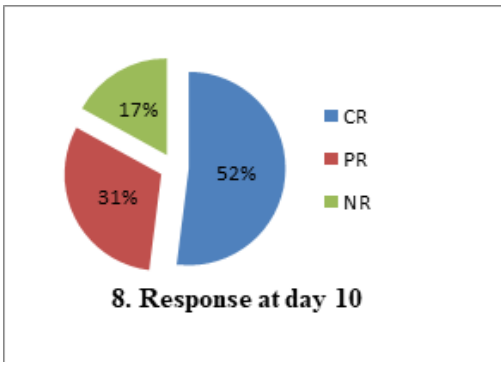
E) Baseline platelet counts

Among 29 patients, 14 patients (48.3%) had platelet count less than 20,000/ mm3, 10 patients (45%) had platelet count between 20,000 and 30,000/ mm3and 5 patients (17.2%) had platelet count 30000-50000/ mm3. The mean platelet count was 21,696 (The minimum platelet count 1000/mm3 and maximum platelet count was 48000/mm3) with standard deviation of 12,394.



F) Platelet counts and bleeding symptoms: When we saw the platelet count and bleeding symptoms, 7 out of 14 (50%) patients with platelet counts less than 20,000/mm3 had clinically severe bleeding and a couple of patients did not have bleeding symptoms and 8 out of 10 (80%) patients having platelet counts between 20000-30000/ mm3 had clinically severe bleeding.



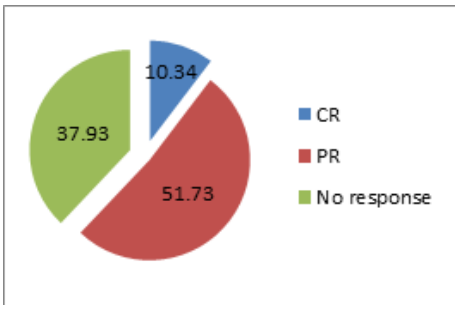


8. Response at day 10

Clinically severe bleeding was seen more in age group 20-40 years. Minor bleeding symptoms seen all patients with age more than 60 yrs.

2. Treatment response evaluation

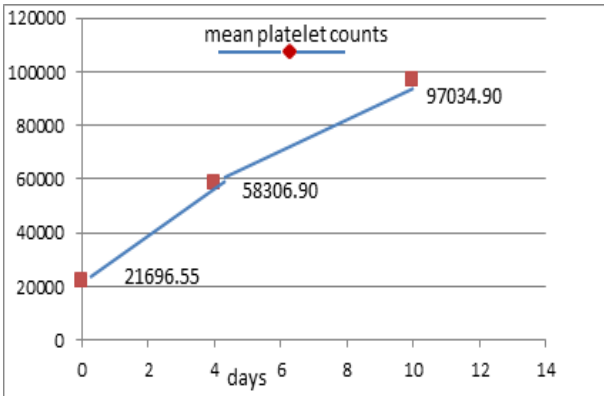
A) Treatment response evaluation at day 4: After the completion of 4thday dose of dexamethasone, there was significant difference (P<0.001) in mean platelet count increased from baseline mean platelet counts 21696 mm3 to 58306 mm3. Out of 29 patients, 18 patients (62%) showed good treatment response (Complete response 10% and partial response 52%) and 11 patients (38%) did not show response. However, there was no significant difference in male and female (P=1) response.



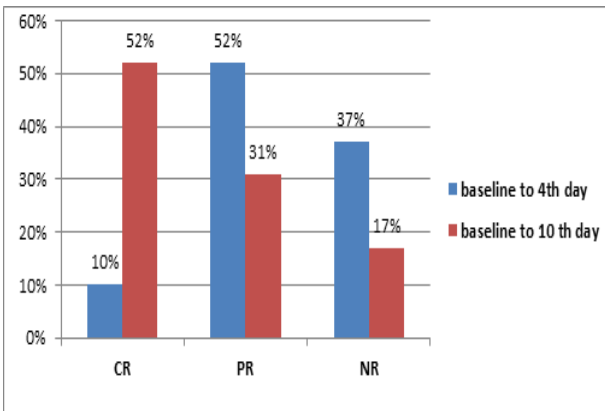
b) Treatment response evaluation at day 10: Complete response achieved in 15 patients (52%). The overall treatment response (CR+PR) seen at day 10 was 83%. Five patients (17%) participants did not show response. The mean platelet count was 97,034/ mm3, difference in platelet count was significantly increased from baseline (P<0.001) and not from day 4 (P=0.16). There was no significant difference in male and female (P-1) response at day 10.

3. Comparison of response

A) Comparison of mean platelet counts: The base line mean platelet count was 21,696/ mm3 which were increased to 58306/ mm3 at day 4. From mean platelet count at day 4 increased to 97048/ mm3 at day 10.



B) Comparison of CR, PR, NR between day 4 and day 10: The complete response at day 4 was seen in 10% of patients. It was 52% of patients at day 10. Where as partial response was 52% and 31 % at day 4 and day 10 respectively. Among the 38% of non-responders at day 4, more than half responded at day 10. There is no significant difference in response (p=0.16)



C) Comparison of response between male and female; There was no significant difference in response (p = 1) seen between male and female at day 4 and at day 10.

4. Other parameters

There was significant difference (P<0.001) in mean leucocytes count from the baseline. The base line leucocytes count was 9817/mm3 which was increased to 13600/mm3. There were no significant difference in hemoglobin, (P=0.62) random blood sugar (P=0.29) and systolic blood pressure. (P=0.37)

5. Side effects evaluation

Twenty five (86.2%) patients did not complain of side effects. Two patients complained increased appetite and one patient had hyperglycemia and one patient complained insomnia.

DISCUSSION

Basis of this study was to determine response of initial cycle of pulse high dose dexamethasone therapy in new cases of primary immune (idiopathic) thrombocytopenia.35 new cases of ITP were registered in Bir hospital during the study period. This number of patients was more than the patients in previous year.[16] This could be because of increased referrals from outside of the valley since more than half patients were from different (16) districts of Nepal.

In this study the number of female patients was higher than male. Among the total 35 patients, 45.7% male and 54.3% were female with male to female ratio 1:1.2. This finding was consistent with previous study carried out by Neylon AJ. Saunders PW, Howard MR et al. who presented the results of a prospective study in a population-based cohort of newly presenting adults with ITP that consisted with male female ratio 1:1.2 among 245 newly diagnosed ITP.[3] Reports on the mean age of presentation of ITP in adult population were variable in different study. In our study, the mean age of the study population was 33.2 years with a standard deviation of 14.8 years. Observations consistent with this study were Mazzucconi MG and his groups who found that the mean age of the 37 patients with ITP was 34yrs in their study.[14] and Pamuk GE, Pamuk ON, Başlar Z et al analyzed retrospectively 321 adults with ITP and found that the median age at diagnosis was 34 yrs.[17] However, in contrary to our findings, a study carried out by Frederiksen H. Schmidt K, the median age was 56 years among the 221 adult patients with ITP,[18] and Cheng, Wong RS, Soo YO et al reported the mean age was 46.7years in their study of 125 adults with ITP.[13] Stasi, R. Stipa E,Masi M et al reported median patient age was 44 years at the time of diagnosis of 208 adults with ITP in their long-term observation.[19]

When the study population was subdivided according to various age groups the maximum number of participants was in the age group of 20 -40 years (57%). The least number of participants were more than 60yrs of age (8%) contrary to findings of Neylon AJ. Saunders PW, Howard MR et al.[3]

Bleeding manifestation was the main presenting feature among the adults with ITP. The general agreement is that the lower the platelet counts higher the bleeding severity and higher the age severe the bleeding. According to bleeding grades laid by WHO, 93% had bleeding symptoms and 7% did not have any bleeding symptoms and were found during the routine investigation for other reason. Clinically severe bleeding symptoms were seen in 55% among them 21% had severe mucosal bleeding and required blood transfusion. Mazzucconi MG and their associates found in their monocentre study that 81% had bleeding symptoms and 16% have severe bleeding symptoms.[14]

When the treatment response of a four-day course of dexamethasone was evaluated, Anderson was the first to document high rates of increased platelet counts of baseline from 12000 + 8200 to 248000 + 130000 per micro liter in all 10 ITP patients.[12] Such a high response was not found in this study. However, after the completion of 4th dose of dexamethasone, there was significant difference (p<0.001) in mean platelet counts which increased from baseline 21,696 to 58,306 per micro liter. More than 60% the patients showed treatment response (Complete response 10% and partial response 52%) to dexamethasone and 37% of patients did not show response. However there was no significant difference seen in male and female response (P-1).

Treatment response evaluation at day 10 showed the mean platelet count was 97.034 per micro liter. The difference in platelet count was significantly increased from baseline (P<0.001) but not with day 4 (P=0.16). Complete response achieved in 52% of patients. The overall treatment response (CR+PR) seen at day 10

was 83.0% of patients. However 17% participants did not show response to dexamethasone. There was no significant difference in response in male and female (P-1) at day 10. Response rate between genders were similar. These findings were similar to the previous reported response of high dose dexamethasone therapy. Cheng Y,Wong R. S, Soo Y. O et al found good initial response to high-dose dexamethasone where the mean (+/-SD) platelet count before treatment 12,200+/-11.300 per cubic millimeter was increased by at least 20,000 per cubic millimeter by the third day of treatment in 106 of the 125 patients (85%) and the mean (+/-SD) platelet count was 101,400+/-53,200 per cubic millimeter one week after the initiation of treatment.[13] Borst.F. Keuning JJ, van Hulsteijn H used high dose dexamethasone as first line therapy in 18 adult ITP patients and found that 83% of patients had a rise in platelet count above the threshold level of 50 × 109/l within days after start of the first course of dexamethasone.[20]

A prospective study conducted by Mazzucconi MG, Fazi P, Bernasconi S et al, a GIMEMA experience, reported of the monocentre study of 37 patients with ITP, in which response rate was 89.2% that was higher than our findings.[14] In this study complete response was achieved in 15 patients (52%) which is similar to the findings of Naithani R. Mahapatra M. Kumar R et al. They carried out a prospective study comparing high dose dexametasone in acute and chronic ITP. They found that high dose dexamethasone therapy showed better responses in acute immune thrombocytopenia than in chronic immune thrombocytopenia. Of twenty-nine enrolled patients overall 20 patients (69%) responded: complete response (CR) was achieved in 16 (55%).[21] However partial response (PR) was higher in our study 31% versus 14%.

Apart from above mentioned findings, the treatment response between day 4 and day 10 after the initiation of high dose dexamethasone was also compared. Though there was increase in platelet counts from day 4 to day 10, it was statistically insignificant. One patient who achieved complete response at day 4 relapsed at day 10. There were no sufficient studies done previously regarding comparison of response between 4th and 10thday. There was no difference in response in male and female patients. Another finding which does not have much study in high dose dexamethasone treatment was leucocytosis. There was significant ($P<0.001$) rise of leucocytes after the therapy. Similar to previous study, side effects were minimal and well tolerated apart from one patient who developed hyperglycemia.

LIMITATION

This study was carried out in a small number of patients. It was single centre study with heterogeneity of patient population including all registered patients during the study period were taken into account.

CONCLUSION

High dose dexamethasone has shown to be an effective first-line treatment for Nepalese adults with immune thrombocytopenia resulting in excellent response within days. There was no correlation with gender, smoking, platelet counts, and severity of bleeding. Thus high dose dexamethasone can be used as a simple tool to obtain a fast rise of the platelet counts in newly diagnosed ITP patients prior to other treatment modalities.

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