Comparison of Low-Dose versus Conventional-Dose Prednisolone in the Treatment of Idiopathic Thrombocytopenic Purpura (ITP)

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Objective: To assess the efficacy of low-dose prednisolone in patients with ITP.

Design: A Prospective Randomized Controlled Trial.

Setting: Salmaniya Medical Complex, Kingdom of Bahrain.

Method: A randomized controlled trial was conducted comparing the conventional-dose to a low-dose of prednisolone (0.25 mg/kg/day).

Forty-one patients with ITP were enrolled in the study; 21 patients were randomized to low-dose prednisolone (group I) and 20 patients received the conventional-dose (group II).

Result: The overall remission rate (OR) for both groups was 78.05%. There was no statistically significant difference between both groups in terms of group overall remission 17 (81%) versus 15 (75%), group complete remission 11 (52.4%) versus 10 (50%) or partial remission rate 6 (28.6%) versus 6 (25%). In addition, failure rate, relapse rate, and splenectomy rate were similar and not statistically significant. Two (10%) patients developed complications related to steroids therapy, both were in group II, but were not statistically significant.

Conclusion: Although the study had a small number of patients, it revealed that low-dose of prednisolone (0.25 mg/kg/day) is as effective as the conventional-dose (1 mg/kg/day) and probably, safer.

Accordingly, we recommend the use of low-dose prednisolone as initial therapy for ITP rather than the high-dose.

Idiopathic thrombocytopenic purpura (ITP) is a relatively common disease, with an incidence of 2.25-6.6/100,000/year[1-3]. Until recently, the main pathology of ITP was thought to be due to autoantibodies attached to the platelets causing their destruction by reticuloendothelial systems, particularly the spleen; however, defective thrombopoiesis and T-cell mediated platelets destruction have been discovered[4-6]. The natural history of ITP is scantily defined, but some studies showed that they had a good outcome and mortality equal to the general population while having more morbidity from the treatment rather than the disease[7-12].

Bleeding is usually uncommon in ITP except in severe cases (platelets count$<30 \times 10^9$/l) and clinical presentation varies from asymptomatic, mild bleeding or serious bleed like intracranial hemorrhage. Patients with platelet counts $>50 \times 10^9$/l need no treatment except if they are undergoing procedures expected to induce blood loss. Steroids and immunoglobulins are considered as first-line therapy, although there are no randomized trials addressing their use versus no treatment[7,8,13]. Splenectomy is reserved for those who fail steroid therapy. Few randomized trials comparing the conventional-dose of prednisolone (1 mg/kg/day) versus the low-dose (0.25-0.5 mg/kg/day) showed no significant difference[1,3,8,12,14-17]. Although, prednisolone in the conventional-dose is still recommended as the initial therapy[2].

The aim of this study is to assess the efficacy of low-dose prednisolone (0.25 mg/kg/day) compared to conventional-dose (1 mg/kg/day) in patients with ITP.

METHOD

Patients diagnosed with ITP from January 2003 to December 2005 were recruited in the treatment protocol. ITP was diagnosed according to the accepted criteria: isolated thrombocytopenia with platelets count below 150×10^9/l, normal hemoglobin level, white blood cell counts, differentials, and peripheral blood smear. In addition, history and physical examinations were not suggestive of any other diseases. Bone marrow examination was not routinely performed. Written informed consent was obtained from each patient. The study was approved by the local ethical committee.

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Patients were treated with 1 gm IV methylprednisolone once daily for three days. On day 4, patients were randomized to either group I who received low-dose prednisolone (0.25 mg/kg/day) or group II who the conventional therapy 1 mg/kg/day. Both treatment modalities were continued for four weeks and then gradually tapered to be discontinued over the fifth week. Patients with serious bleeding (CNS or GIT) could receive intravenous immunoglobulin irrespective of randomization (1-2 gm/kg total dose over 1-5 days); however, none of the patients had severe bleeding that warrants this intervention. Figure 1 shows a summary of the flow of participants through each stage of randomization.
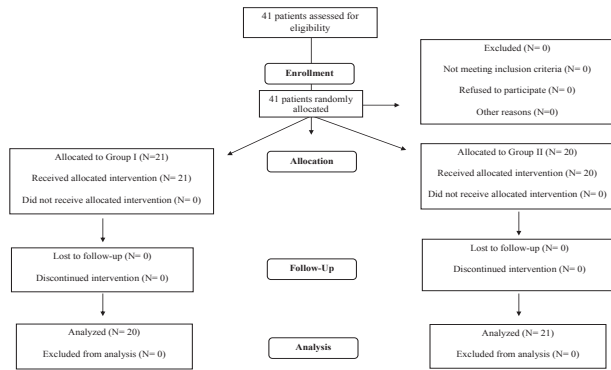

Figure 1: Randomization of Low-Dose and High-Dose of Prednisolone in Idiopathic Thrombocytopenic Purpura

Patients with platelet count more than 50×10^9/L, patients with secondary ITP including drug-induced ITP or patients who received steroid therapy before admission were excluded. However, the virus associated ITP such as HIV, hepatitis B and C and EBV were included.

Follow-up was arranged for all patients monthly for the first year, quarterly for the second year, then once every six months for the third year and then annually. The mean follow-up for all patients was 11 months, 5-24 months. None was lost to follow-up. Patients were assessed clinically and complete blood count (CBC) was performed.

Complete remission (CR) was defined as platelet counts of $\geq 150 \times 10^9$/L, while partial remission (PR) was considered when platelet counts are $\geq 50 \times 10^9$/L but $<150 \times 10^9$/L. Death or failure to achieve CR/PR after two months of treatment or reduction of platelet counts during tapering down the prednisolone dose were considered treatment failures.

Although, relapse is described as platelet counts $<150 \times 10^9$/L if previously in CR, or $<50 \times 10^9$/L if previously in PR.

Data were analyzed using SPSS 17. The results were analyzed using Mann-Whitney to test differences between means of quantitative variables and Chi-Square to test the differences between proportions of qualitative variables.

RESULT

Forty-one patients were included in the study from January 2003 to December 2005; 29 (70.7%) were females, of which one was diagnosed in the postpartum period, and 12 (29.3%) were males. Twenty-one (51.22%) patients were randomized to low-dose prednisolone (group I) and 20 (48.78%) received the conventional-dose (group II). The mean age for group I was 29 years (range 14-47 years); the mean age for group II was 39 years (range 20-90 years). Clinically, all patients presented

with thrombocytopenia with a mean platelet count of 11×10^9/L and 8.7×10^9/L. None of the patients presented with bleeding. Both groups were matched and homogenous in personal characteristics and clinical features, see table 1.

Table 1: Personal Characteristics and Clinical Features

		Group I	Group II	Total	P-Value
Age range (Mean±SD)		14-47 (29.14±10.19)	20-90 (38.95±17.02)	14-90 (33.93)	0.066[a]
Sex	Male	(% 28.6) 6	12 (29.3%)	6 (30 %)	0.920[a]
	Female	15 (71.4 %)	29 (70.7%)	14 (70 %)	
Pregnant/postpartum		1 (4.76%)	0 (0%)	-	
Mean Platelets count on Admission (R.R.[b] 150-400 x10⁹/L)		11.14±13.73	8.7±7.651	9.95±11.12	0.854[a]

[a]not significant
[b]reference range

The OR for both groups was 78.05%. There was no statistically significant difference between both groups in terms of group specific OR (81% versus 75%, P=0.645), group specific CR (52.4% versus 50%, P=0.879) or PR (28.6% versus 25%, P=0.92). None died, although 8 (19.5%) patients failed to achieve remission, four patients in each group; five (12.2%) of them subsequently had splenectomy and achieved complete remission, while the remaining responded to the second course of steroid. Nevertheless, the difference was not statistically significant comparing the two regimens.

Fourteen (34.15%) patients relapsed following a mean response period of 11.14±13.73 months; 6 (28.6%) in group I and 8 (40%) in group II. Once again, the difference was not statistically significant, P=0.92. Overall, 13 (31.7%) patients had splenectomy to maintain adequate platelet counts 6 (28.6%) in group I and 7 (35%) in group II. There was no statistical difference between both groups whether we consider splenectomy rate following treatment failure or consequent to relapse.

Two patients developed complications related to steroids therapy. One developed ischiorectal abscess and the other one developed hyperglycemia and glaucoma, both were in group II, and none of group I developed any complications related to steroid; still, these were statistically not significant, see table 2.

Table 2: Patients Outcome

Outcomes		Patients	Group I	Group II	P-Value
Complete remission (CR)		21 (51.2)	11 (52.4%)	10 (50%)	0.879[a]
Partial remission (PR)		11 (26.8%)	6 (28.6%)	5 (25%)	0.920[a]
Overall remission (OR)		32 (78%)	17 (81 %)	15 (75%)	0.645[a]
Failure		8 (19.5%)	4 (19%)	4 (20%)	0.627[a]
Death		0 (0%)	0 (0%)	0 (0%)	NA[b]
Relapse rate (RR)		14 (34.15%)	6 (28.6%)	8 (40%)	0.438[a]
Complications	Infection		0 (0%)	1 (5%)	NA[b]
	Increased intraocular pressure		0 (0%)	1 (5%)	
	Hyperglycemia		0 (0%)	1 (5%)	
Splenectomy		13 (31.7%)	6 (28.6%)	7 (35%)	0.658[a]

[a] not significant
[b]not applicable

DISCUSSION

ITP is an autoimmune disease which is benign in nature; less than 5% run a severe chronic course which dictates a difficult management approach[3,7-12].

Prednisolone at a dose of 1 mg/kg/day is used as initial therapy for ITP by many experts since the recommendations by Dameshek et al in 1958[3,18-20]. However, the role of prednisolone at this dose, the duration of the therapy, rate and sustainability of the remission is not clear[3,7,8,10,16,17]. In addition, the role of steroid in the natural course of the disease is also doubtful[7,8,10,11,13].

Moreover, several studies addressed and compared the conventional-dose of steroid versus low-dose (between 0.25-0.5 mg/kg/day) and showed no significant difference between the regimens[8,12,14-17].

Bellucci et al found no significant difference in response rate or rapidity of response in adults with acute ITP to low-dose of prednisolone (0.25 mg/kg/day) versus conventional-dose (1 mg/kg/day)[14]. Similarly, Mazzucconi et al reported no significant difference in remission rate between high-dose prednisolone (1.5 mg/kg/day) and low-dose prednisolone (0.5 mg/kg/day)[16].

Several studies compared conventional and low-dose of prednisolone reported no significant difference in remission rate; however, these were in non-English language and only abstract were available in English[15,16].

We found no statistically significant difference in the rate of remission between the two groups, whether considering overall remission (OR), complete remission (CR) or partial remission (PR), which was similar to the finding in the study by Bellucci et al and others[3,8,12,14-17,21].

Our study recommends the use of low-dose because it is not resulting in more failures. Furthermore, those failures responded to a second course of the same dose of prednisolone or Splenectomy without any significant complications.

Fourteen patients (34.15%) had relapsed during a mean follow-up period of eleven months; this is comparable to other reported studies, although there were six relapses in group I and eight in group II; however, these were not statistically significant[7-12].

Two patients in group II developed complications related to steroid therapy, one had an ischiorectal abscess and the other patient developed hyperglycemia and glaucoma while none of group I developed any complications. This was not statistically significant because of the small number of patients; however, it shows that high-dose is associated with more complications[22].

It may be argued that initial use of methylprednisolone at 1g/day for 3 days contributed to the results achieved in our study; however, this dose for very short duration would not affect the course of the disease. Moreover, no study showed that this dose and duration of methylprednisolone has any significant effect in the natural course of ITP.

The rate of Splenectomy was comparable in both groups indicating that low-dose prednisolone did not increase the need for Splenectomy.

CONCLUSION

This study, though it has a small number of patients, showed that low-dose of prednisolone (0.25mg/kg/day) is as effective as the conventional-dose (1mg/kg/day).

The high-dose prednisolone is more expensive and is associated with more complications compared with low-dose and eventually, it would reduce the burden on health services.

Therefore, we recommend the use of low-dose prednisolone as initial therapy for ITP rather than the high-dose.

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