Original Research Article

Efficacy of high dose pulse methylprednsiolone (somidex) vs oral prednisolone for treatment of newly diagnosed idiopathic thrombocytopenic purpura in Rajavithi hospital: open labelled randomized controlled trial

Abstract

Background ITP is a disease which develops as a result of increased activity of the reticuloendothelial system (mainly the liver and spleen). The role of high-dose short- acting corticosteroids in the treatment of immune thrombocytopenic purpura in adults is controversial. We assessed the effectiveness of high-dose corticosteroids, compared with that of standard oral prednisolone therapy, for initial treatment of adults with immune thrombocytopenic purpura.

Methods 52 patients were randomized to receive pulse methylprednisolone (1gm/day) for 3 days, or oral prednisolone 1 mg/kg/day for 84 days. Response was evaluated at D10/D14/D28 and at the end of treatment on D84. Degree of response was evaluated in term of platelet count number and duration of response.

Results The mean initial platelet count was 28,031.58+ 23,663.61 per cubic millimeter. Of these 52 eligible patients, about two thirds had an initial response to pulse methylprednisolone. Seventeen of the 26 patients (65%) on oral prednisolone responded to steroids on D10, and this was identical to the number of initial response patients in the methylprednisolone arm. At the end of the 3rd month of therapy, 20/26 (76.9%) those with methylprednisolone were still in complete response (platelet count more than 100,000/uL) compared with 20/24 (83.3%) patients in the oral prednisolone arm. Although mean platelet count in oral prednisolone group were slightly significantly higher than those of methylprednisolone group on D10, D14, D28 and at the end of study after treatment, platelet count was in complete remission in both arms. Life threatening side effects were more in those with oral prednisolone arm (4 cases), as compared with high dose pulse methylprednisolone,which is no grade 3,4 side effects.

Conclusion The high-dose pulse methylprednisolone is not more effective than standard-dose oral medication during the study period. It is worth considering high dose pulse methylprednisolone for newly diagnosed chronic ITP patients who seem to be unable to tolerate the long-term side effects of standard oral corticosteroids and need a short response time.

Key words: ITP, methylprednisolone (somidex), Idiopathic Thrombocytopenic Purpura, oral corticosteroids

Introduction

ITP is a disease which results from increased activity of the liver and spleen in destroying autoantibody-coated platelets. The standard first-line treatment of this disease is corticosteroids, which generally have a success rate of approximately 60-70%[1]; however, most patients suffer relapse after the first line of treatment, and they also encounter side effects from high doses of corticosteroids aimed at achieving durable and sustained response in order to maintain an acceptable platelet count (at least 30,000/uL), Second-line therapies have diverse impacts on response for relapsed/refractory patients, and also a variety of side effects. Nowadays, there are several new treatments and drugs available for this condition, including pulse methylprednisolone, high-dose dexamethasone, antiCD20 (rituximab), immunosuppressive agents, anabolic steroids and eltrombopag. Some novel therapies with lower side effects are available; however, these are costly and require long-term treatment. Methylprednisolone is one of the salvage treatments recommended for patients refractory to standard oral prednisolone, and it has fast onset of action. Short courses of "pulsed" high-dose corticosteroids in the form of methylprednisolone 1-3 gm have already been proven to be effective in treatment for relapsed and refractory cases. Some of ITP is an emergency condition requiring immediate hospitalization. Guidelines for the treatment of ITP is important. Short and effect treatment protocol for this condition is mandatory for the doctors and may be used as an effective alternative therapy in term of limited time and resources.

In Thailand, we have limitations in our budget for using new costly therapies, and high-dose corticosteroids (methylprednisolone) are suitable for use in our context. Its duration of response and maintenance of adequate platelet numbers with low risk of side effects for a period of time render it appropriate for follow up and monitoring of our patients. This study was designed to compare the efficacy of a short course of methylprednisolone with that of standard oral prednisolone in newly diagnosed patients. We evaluated response rate, duration of response and the side effects of this approach compared with those achieved by standard treatment.

Methods

Selection of patients

Consecutive patients at Rajavithi Hospital in Bangkok who were newly diagnosed with idiopathic thrombocytopenic purpura between January 2018 and December 2020 and required treatment were enrolled in this study. Immune thrombocytopenic purpura was diagnosed by clinical presentation, laboratory examination, and bone marrow study. All patients had either platelet count of lower than 30,000/uL or clinically significant bleeding. The criteria for exclusion were: previously diagnosed ITP; prior treatment with corticosteroids for 6 months; history of clinically significant side effects of corticosteroids; positive serology for HIV, HCV or HBV; pregnancy; or immunocompromised status that precluded the use of corticosteroids. We chose to conduct a randomized controlled trial to assess the superiority of treatment with pulsed high-dose corticosteroids over that of oral standard prednisolone (1mg/Kg/day).

Treatment protocol

The block of four randomization was generated for the randomization process. Enrolled patients were randomized on a 1:1 basis to receive either consecutive 3-day courses of pulse methylprednisolone (1gm) or oral prednisolone 1 mg/Kg/day for 3 months. The three criteria for initial response were an increase in platelet count of at least 30,000/uL, platelet count of at least 50,000/uL by D10 after initiation of treatment, and cessation of bleeding. Unresponsiveness was defined as an increase in the platelet count of less than 30,000/uL or a platelet count of 50,000/uL or less by D10. Other treatments were considered if there was no response to either therapy. If the patient had a platelet count of more than 50,000/uL after D10, no further treatment was given in the pulsed methylprednisolone group. The patients were followed up on D10/D14/D28 and D84, and a sustained response was defined as a platelet count that remained above 50,000/uL after 3 months (D84) of follow up. In the oral prednisolone group, the patients received 1 mg/Kg/day until D84 unless untolerated (grade 3 or 4) side effects from corticosteroids were detected, or in cases of failure to achieve at least sustained response in platelet count. In the event of untolerated side effects or unresponsiveness, the patients were given proper

salvage treatment in accordance with Thai guidelines for treatment of ITP. All patients had followed up to monitor platelet count and clinical bleeding after completion of the two treatments.

Laboratory studies

Complete blood counts were obtained at: recruitment; on D10, D14, D28, and D84 of treatment; and during follow-up visits. Fasting plasma glucose levels were measured at recruitment, during treatment, and at follow-up visits. Blood pressure, body weight and serologic test for HIV, HCV and HBV were performed at the time of recruitment. Chest X ray was used to screen possible TB infection, and in the case of suspected lesions on radiologic study, a confirmatory test for TB was performed. Premenopausal women were screened for pregnancy with urine tests. Bone marrow biopsy and aspiration were conducted in all cases to exclude other secondary causes of thrombocytopenia.

Outcomes

The primary outcome was to compare the response rates of patients in the pulse methylprednisolone (somidex) arm with those of their counterparts in the control arm receiving standard oral prednisolone.

Secondary outcomes were the number of patients who needed salvage therapy, and the side effects resulting from the two treatment regimens.

Statistical analysis

The groups of patients with a sustained platelet response at 3 months and the groups of those who had relapse at six months were compared with respect to age, sex, and platelet count before treatment; on D10, 14, and 28, as well as 3 months after completion of treatment. This comparison was made to determine whether these variables were predictive of sustained response. Numerical data were compared with the use of Student's t test for independent samples, and categorical data were compared with the use of the chi-square test. Differences were considered to be significant when $p<0.05$. All reported p-values were two-sided, and all other values were mean and standard deviation otherwise indicated. We used IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp, as statistical software to analyse the data.

Sample size calculation

The sample size was calculated using the two-proportion formula (Bernard 2000)[2]. Based on a study by Mashhadi (2012)[3], the 6-month response dexamethasone vs prednisone was 90% vs 53.3%. Type I error was 5%, and the power of the test was 80%. The subjects exposed equally to each group were 23 samples with an anticipated dropout rate of 15%. Consequently, the total number of cases required in the study was 52.

Results

Patient characteristics

Between 2018 and 2020 at Rajavithi Hospital, Bangkok, 52 patients with newly-diagnosed immune thrombocytopenia were enrolled in this study. The subjects were aged between 15 and 88 years old, their mean age was 48.15$\pm$23.11 years (mean$\pm$SD), 35 were male and 17 were female. Patients in the two groups were classified by sex, age and underlying comorbid diseases, as shown in Table 1. Most patients in both groups had diabetes, essential hypertension, or both as comorbid illnesses. Other comorbid illnesses included chronic kidney disease, gout, chronic demyelinating polyneuropathy, migraine, and stroke, as shown in

Table 1 Patient's characteristics

Characteristics	Somidex (n=26)	Steroid (n=26)	p-value
Age; years			0.481
mean±SD	51.78±19.60	46.80±23.11	
Median (min, max)	40.50 (15, 88)	46.50 (20, 82)	
Gender			0.768
Male	9 (34.6)	8 (30.8)	
Female	17 (65.4)	18 (69.2)	
Underlying			
DM			1.000
Yes	4 (15.4)	4 (15.4)	
No	22 (84.6)	22 (84.6)	
HT			1.000
Yes	2 (7.7)	2 (7.7)	
No	24 (92.3)	24 (92.3)	
DM/HT			0.490
Yes	0 (0.0)	2 (7.7)	
No	26 (100.0)	24 (92.3)	
Gout			1.000
Yes	1 (3.8)	0 (0.0)	
No	25 (96.2)	26 (100.0)	
ESRD			1.000
Yes	1 (3.8)	1 (3.8)	
No	25 (96.2)	25 (96.2)	
CIDP			1.000
Yes	1 (3.8)	0 (0.0)	
No	25 (96.2)	26 (100.0)	
Migraine			1.000
Yes	1 (3.8)	0 (0.0)	
No	25 (96.2)	26 (100.0)	
Stroke			1.000
Yes	0 (0.0)	1 (3.8)	
No	26 (100.0)	25 (96.2)	

DM: Diabetes mellitus, HT: Hypertension, ESRD: End stage renal disease, CIPD: Chronic inflammatory demyelination disease

Response to therapy

The mean platelet count before treatment was 28,031.58± 23,663.61 per cubic millimeter (mean±SD) (range, to per cubic millimeter). Of these 52 eligible patients, about two thirds had an initial response to pulse methylprednisolone. Seventeen of the 26 patients (65%) on oral prednisolone responded to steroids on D10, and this was identical to the number of initial response patients in the methylprednisolone arm. At the end of the 3rd month of therapy, 20/26 (76.9%) patients who were treated with methylprednisolone were still in complete response (platelet count more than 100,000/uL) compared with 20/24 (83.3%) patients in the oral prednisolone arm.

Table 2 Response results as compared by date of treatment

Characteristics	Somidex (n=26)	Steroid (n=26)0	p-value
Age; years			0.481
mean±SD	51.78±19.60	46.80±23.11	
Median (min, max)	40.50 (15, 88)	46.50 (20, 82)	
Gender			0.768
Male	9 (34.6)	8 (30.8)	
Female	17 (65.4)	18 (69.2)	
Platelet			
D0	25,555.56±28,259.77	30,550.00±21,830.63	0.544
D10	119,333.33±74,273.74	114,315.79±86,149.13	0.850
D28	114,823.53±87,707.78	127,285.71±106548.96	0.723
D84	140,937.50±96,788.75	173,900.00±72,076.27	0.364

Plus-minus values are means±SD

In the methyl prednisolone arm, 6 patients did not attain complete response. Three patients were without clinical signs and symptoms of active bleeding with platelet counts of 60,000, 40,000 and 61,000/uL,respectively. Another 3 patients needed salvage therapy for thrombocytopenia and/or active bleeding including 1 platelet transfusion and IVIg, while 2 needed to start prednisolone 1 mg /kg/day. One patient died from septicemia after D84 of treatment.

In the oral prednisolone arm, 6 patients were unresponsive: 2 died after day 10 of treatment due to septic shock from gram negative bacteria and pneumonia; 1 needed salvage with IVIg, platelet transfusion and anabolic hormone during the 3 months of treatment; 2 had to add on immunosuppressive drugs and platelet transfusion; and 1 survived with add-on immunosuppressive therapy and a tapered dose of prednisolone due to intolerable side effects of hyperglycemia.

Side effects

No patients in the methylprednisolone arm succumbed to complications during the 3 months of treatment; however, 2 in the oral prednisolone therapy group died, 1 from gram negative septicemia, and 1 from pneumonia. Side effects among patients in the methylprednisolone arm included grade 1 and 2 hypotension during infusion of medications. Of the patients who received oral prednisolone for 3 months, 2 had proximal muscle weakness grade 3 and 4, 1 had neuropsychiatric depression, and 1 developed uncontrolled hyperglycemia. These patients needed adjustment of prednisolone during therapy, as shown in Figure 1.

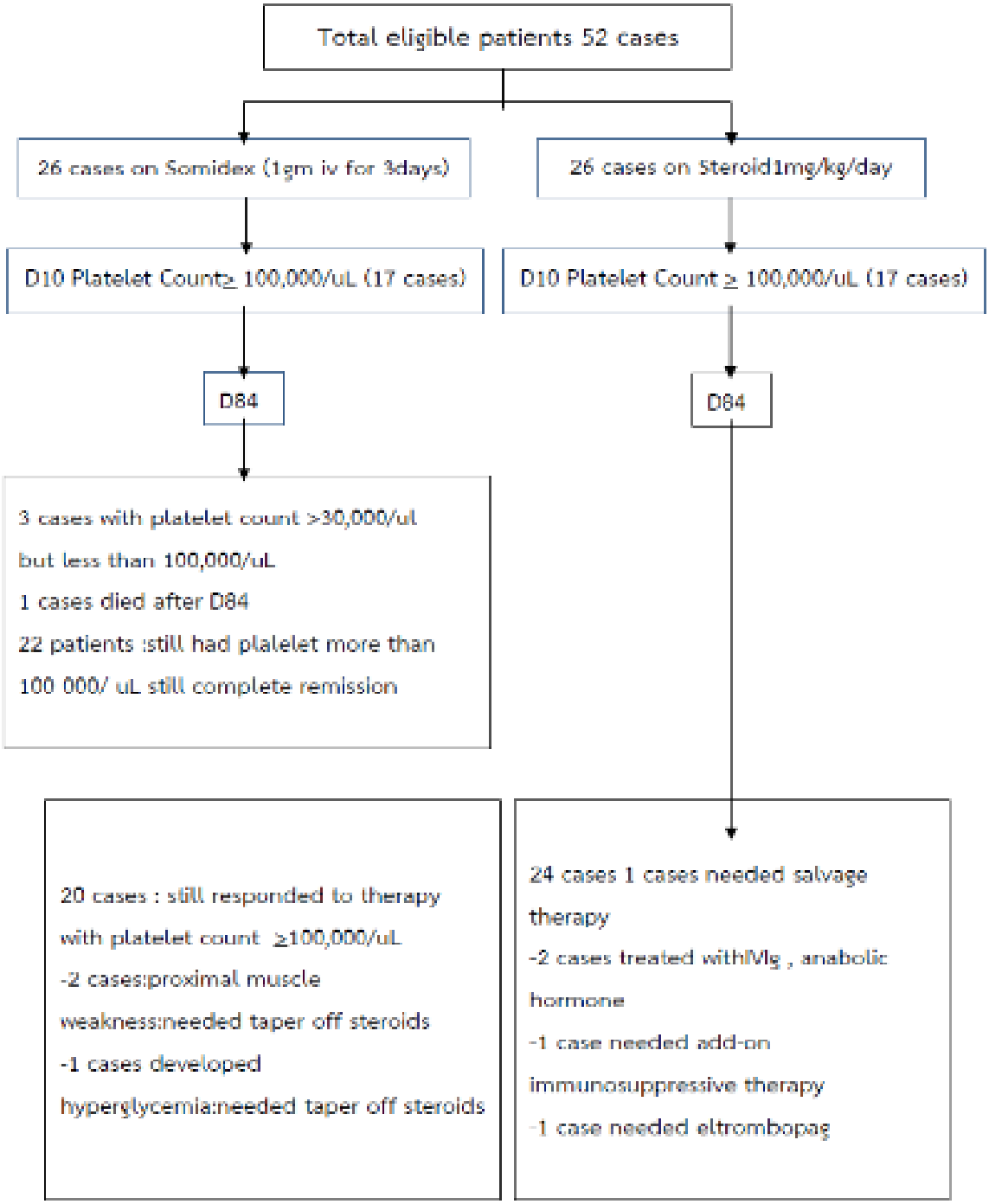

Figure 1 treatment protocol and results in all 52 pateints with newly diagnosed immune thrombocytopenia

Discussion

For adults with newly-diagnosed ITP with platelet count of less than 30,000/uL, the guidelines recommend treatment even in the absence of mucosal bleeding[4]. The use of IV pulse methylprednisolone for 3 consecutive days has been tried in treatment of chronic ITP in children, with a response rate of 90% (complete response after 3 months)[5]. Recommnedation by international concensus on 2019[6], methylprednisolone is one therapeutic option for newly diagnosed patients. Since 2000,There were only 2 scientific studies confirmed its efficacy in first line setting[7-8]. To reduce the burdens of healthcare personnels and deliver effective short course of therapy,we aimed to determine the possibility of using a short course of high-dose pulse methylprednisolone as first-line therapy for newly diagnosed adult ITP patients, instead of a 3-month course of standard dose oral prednisolone. Intravenous high-dose therapy yields the benefit of inducing a rapid increase in platelet count as effectively as oral corticosteroids; however, not only does it require intravenous infusion for 3 days and monitoring of side effects during infusion, but it also achieves a more transient response. Its common side effects are basically the same as those of oral corticosteroids; however, unlike oral corticosteroids, it caused no grade 3 or 4 side effects in the high-dose therapy arm during our study's 3-month period whereas patients in the oral therapy group needed a reduction in dose of oral corticosteroids.

Albayrak et al. compared IVIG (0.5 g/kg/day for 4 days) and methylprednisolone (30 mg/ kg/day or 50 mg/kg/day for 7 days, oral) in the treatment of acute ITP, and could not find any difference as for increase in platelet counts.[9] Tarantino et al. compared IVIG and anti-D treatments, and similarly reported lack of any statistically significant difference.[10] Erduran et al. compared oral methylprednisolone (30 mg/kg/day for 3 days, and 20 mg/ kg/day for 4 days) with IVIG treatments, and found similar effects of both medications in the acute treatment of ITP.[11] In our study, when the high steroid treatment was given as divided doses and daily flat dose (3 consecutive days regimen), the fact that the time to increase the platelet counts above 20,000/mm3 was found to be indifferent supports this route of administration of this treatment.

As mentioned on figure 1., there were no unacceptable toxicities between 2 groups. Its lack of toxicity, short duration of treatment, low cost, and rapid increase in platelet count make this a safe initial treatment, offering a good chance of remission. Initial response rates with this approach range from 70-80%; however, a high incidence of relapse results in low long-term remission rates. Moreover, data is emerging regarding shorter courses of high-dose steroids, such as dexamethasone, which has shown promising results in treatment of ITP. Neither overall response rates nor complete response at 6 months are significantly different between dexamethasone and prednisone. (OR =54%vs43%, relative risk(rr)=1.16,95%confidence interval, [CI] 0.79-1.41, P=.44; CR=37%vs21%, rr=1.49,95%CI 0.5-4.48, P=.48)[12]. In our study,overall complete response rate at 3 months in the IV high-dose treatment was still higher at 85% (22/26) in comparison with that of the standard oral prednisolone group (77% (20/26)). Adverse events were comparable in the dexamethasone and oral prednisolone arms. In general, adult ITP follows a chronic course, so that long-term use of corticosteroids inevitably causes side effects. In our study, response rate at initial treatment (D10) was higher but identical for both arms. At 3 months after treatment commencement, response and sustained response rates were still high, but salvage therapy was required in the long term for both groups. Our patients in chronic steroid use treatment arm only reported acceptable side effects,such as dyspepsia, lethargy, mental problems . All side effects improved after tapering dose of oral steroids. Only 3 from 26 patients(<1%) had serious side effects from oral steroids ,which were also improved after tapering dose. However,There are no new data since 2010 to recommend methylpredniso(lo)ne over dexamethasone or prednisone.

It is worth considering this first-line treatment for newly-diagnosed chronic ITP patients who seem to be unable to tolerate the long-term side effects of standard oral corticosteroids and need a short response time. Moreover,this protocol delivered short and effective treatment to reduce healthcare personnel burden without increased toxicities.

Conclusion

The high-dose pulse methylprednisolone is not more effective than standard-dose oral medication during the study period. It is worth considering high dose pulse methylprednisolone for newly diagnosed chronic ITP patients who seem to be unable to tolerate the long-term side effects of standard oral corticosteroids and need a short response time.

Ethical Approval and Consent:

Written informed consent was obtained from all patients. This study was approved by the Research Ethics Committee, Rajavithi Hospital (COA No. 069/2560).

Disclaimer (Artificial intelligence)

I hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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