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# The clinical effect of Prednisone in combination with Mycophenolate mofetil on idiopathic thrombocytopenic purpura (ITP) and its influence on the level of peripheral blood T lymphocytes and NK lymphocytes

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## ABSTRACT

**Objective:** To explore the curative effect and safety of Prednisone in combination with Mycophenolate in treating ITP and its influence on the level of peripheral blood T lymphocytes and NK lymphocytes.

**Method:** 93 cases of ITP patients were divided into the observation group and the control group by the Random Number Table method, 48 cases for the observation group, 45 for another. Patients in the control group orally took 0.5 mg/kg Prednisone Acetate tablets daily, two times each in the morning and evening. And the observation group, based on the treatment of the control group, orally took Mycophenolate Mofetil Dispersible tablets twice a day, 1 g each time. According to patients' conditions, 3 to 5 courses were set for treatment with 3 weeks a course. Compared PLT amount and the changing situation of inflammatory factors, CD3<sup>+</sup> and CD3<sup>+</sup>CD95L<sup>+</sup> before and after the treatment, the level of CD3<sup>+</sup>Caspase-3<sup>+</sup> and CD3<sup>+</sup>Caspase-8<sup>+</sup>, NK<sup>+</sup>, NK<sup>+</sup>CD95L<sup>+</sup>, NK<sup>+</sup>Caspase-3<sup>+</sup>, NK<sup>+</sup>Caspase-8, the curative effect and adverse events.

**Result:** After treatment, PLT amount in both groups increased, and the increase in the observation group was much higher than that of the control group, the difference had statistical significance ( $P < 0.05$ ). The time needed for PLT amount in the control group to reach the normal and peak values was longer than that of the observation group, whose PLT peak value was higher than another group. The difference had statistical significance ( $P < 0.05$ ). After the treatment, the levels of TNF- $\alpha$  and IL-6 were lowered, and the value of the observation group was lower than that of another. The difference between and within the group has statistical significance. After the treatment, the level of CD3<sup>+</sup>, CD3<sup>+</sup>CD95L<sup>+</sup> and CD3<sup>+</sup>Caspase-8<sup>+</sup> is much higher and CD3<sup>+</sup>Caspase-3<sup>+</sup> level lower than that before the treatment. The difference has statistical significance ( $P < 0.05$ ). After the treatment, the level of NK<sup>+</sup> and NK<sup>+</sup>CD95L<sup>+</sup> is higher and the level of NK<sup>+</sup>Caspase-8<sup>+</sup> lower than that before the treatment. The difference has statistical significance ( $P < 0.05$ ). After the treatment, the total effective rate 91.67% of the observation group is much higher than that 75.56% of another. The difference has statistical significance ( $P < 0.05$ ). After the treatment, the incidence rate of adverse events in the control group is 11.11% (5/45), while 4.17% (2/48) in the observation group. The difference between groups has statistical significance ( $\chi^2 = 3.890$ ,  $P < 0.05$ ).

**Conclusion:** The curative effect of Prednisone in combination with Mycophenolate on ITP patients is better than orally taking Prednisone tablets. Moreover, when it comes to Prednisone in combination with Mycophenolate, both the PLT amount and immunocompetence are improved without much adverse reaction, and the molecules of peripheral blood T lymphocytes and NK lymphocytes can be effectively adjusted to relieve the symptoms. So the method is trustworthy to be popularized for clinical practices.

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## 1. Introduction

Characteristic of the increase or normal amount of megakaryocyte and the reduction of blood platelet, ITP is an unexplained acquired hemorrhagic disease, whose clinical symptoms are visceral hemorrhage, mucocutaneous hemorrhage and the reduction of blood platelet in peripheral blood, thus threatening the life safety of patients (Blanchette et al., 1998; Provan and Newland,



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2002). Although ITP is commonly seen clinically, its pathogenesis remains unclear. There are many ways in which the disease can be treated with much improvement, but no concrete method to eliminate it has been found (Swain et al., 2016). The choice drug for ITP is glucocorticoid, which serves to reduce the production of autoantibody and effectively inhibit immunoreaction, but it has a great adverse reaction (Guenno et al., 2011). Mycophenolate mofetil (MMF), as a new type of immunosuppressor, is widely applied in the treatment like bone marrow transplantation and systemic lupus erythematosus (SLE) (Hannan et al., 2018; Karagoz et al., 2017; Mukattash et al., 2018). The paper, by studying Prednisone in combination with Mycophenolate in treating ITP and its influence on the level of peripheral blood T lymphocytes and NK lymphocytes, aims to provide a reference for the disease.

## 2. Materials and method

### 2.1. General materials

Select 93 cases of ITP patients in our hospital from November 2015 to December 2017 as research objects. After getting the permission of both patients and their families, divide them into two groups, 48 and 45 for each. Among the 93 cases, 59 male cases, 34 female cases with an age from 21 to 56 and 3 to 7 years course of disease. Among the cases in the observation group, 9 cases visceral hemorrhage, 27 mucocutaneous hemorrhage, 12 visceral and mucocutaneous hemorrhage; among the control group, the case number is 7, 23 and 15 respectively. The difference in terms of age, sex ratio and disease severity has no statistical significance ( $P > 0.05$ ). Inclusion standard: those who have signed the consent forms and are in accordance with the strict standard (PLT amount  $< 30 \times 10^9 / L$ ) and ITP diagnosis standard. Exclusion standard: those whose heart, lung and kidney are under unsound conditions; those who have taken drugs that may affect PLT amount within 3 months; those who have sharp immunologic function decline; those in gestation and lactation periods.

### 2.2. Treatment method

Both groups undergo normal clinical care and treatment, which limits their activities, promotes care, avoids injuries and forbids drug-taking that may affect PLT aggregation. On the basis, patients in the control group orally take 0.5 mg/kg Prednisone Acetate tablets daily, two times a day in the morning and evening (Zhejiang Xianju Medicine Co., Ltd, approval number, SFDA approval number: H33021207, specification: 5 mg). On the treatment basis of the control group, patients in the observation group orally take 1 g MMF dispersible tablets twice a day. (Hangzhou Huadong Medicine Co., Ltd, approval number, SFDA approval number: H20052083, specification: 0.25 mg). According to patients' conditions, 3 to 5 courses are set for treatment with 3 weeks a course.

### 2.3. Observation indicator and curative effect evaluation

#### 2.3.1. PLT amount

Observe and record the PLT amount of patients in both groups before and after the treatment, record the time that PLT reaches the normal and peak values during the process, and the PLT at the peak value.

#### 2.3.2. The changing situation of inflammatory factors

Observe and record the changing situation of TNF- $\alpha$  and IL-6 before and after the treatment.

The level of CD3<sup>+</sup> and CD3<sup>+</sup>CD95L<sup>+</sup>, CD3<sup>+</sup>Caspase-3<sup>+</sup> and CD3<sup>+</sup>Caspase-8<sup>+</sup>, NK<sup>+</sup> and NK<sup>+</sup> CD95L<sup>+</sup>, NK<sup>+</sup>Caspase-3<sup>+</sup> and NK<sup>+</sup>Caspase-8<sup>+</sup> before and after the treatment.

#### 2.3.3. Evaluation standard for the clinical effect

Slightly effective: PLT amount becomes normal and clinical symptoms like hemorrhage disappears; effective: PLT amount increases to  $50 \times 10^9 / L$ , clinical symptoms like hemorrhage improve or basically disappears; ineffective: clinical symptoms like PLT and hemorrhage have no improvement but deterioration. Total effective rate = (slightly effective cases + effective cases) / total cases  $\times 100\%$ .

Observe adverse events, which includes hemorrhage aggregation, digestive tract problems, edema, high blood pressure, serious infection, headache or dizziness, liver function changes. And calculate the incidence rate of adverse events.

### 2.4. Statistical analysis

Adopt SPSS 20.0 statistical software,  $\bar{x} \pm s$  for quantity measurement materials,  $t$  for testing.  $\chi^2$  for testing counting materials. The difference has no statistical significance when  $P < 0.05$ .

## 3. Result

### 3.1. PLT comparison before and after the treatment

PLT amount for both groups before the treatment has no significant change ( $P > 0.05$ ); after treatment, PLT amount increases, while the increase in the observation group is more evident, with statistical significance in the difference ( $P < 0.05$ ) See Table 1.

### 3.2. The comparison between the two groups about the time that PLT reaches normal and peak values, and PLT peak values

The time that PLT reaches normal value and peak value is longer than that of the observation group. PLT peak value is further elevated in the observation group ( $P < 0.05$ ). See Table 2.

### 3.3. The changing situation of inflammatory factors in both groups before and after the treatment

Before the treatment, TNF- $\alpha$  and IL-6 of both groups have no statistical significance ( $P > 0.05$ ), while after the treatment, TNF- $\alpha$  and IL-6 are lower. Such indicators are further decreased in the observation group ( $P < 0.05$ ) See Table 3.

### 3.4. The level change of peripheral blood T lymphocyte in both groups before and after the treatment

After the treatment, the level of CD3<sup>+</sup>, CD3<sup>+</sup>CD95L<sup>+</sup> and CD3<sup>+</sup>Caspase-8<sup>+</sup> is higher, while the level of CD3<sup>+</sup>Caspase-3<sup>+</sup> is lower ( $P < 0.05$ ). See Table 4.

### 3.5. The level change of NK lymphocyte in both groups before and after the treatment

After the treatment, the level of NK<sup>+</sup> and NK<sup>+</sup> CD95L<sup>+</sup> is higher, while the level of NK<sup>+</sup>Caspase-8<sup>+</sup> is lesser ( $P < 0.05$ ). See Table 5.

### 3.6. The comparison of curative effect between the two groups

After the treatment, the total effective rate of the observation group (91.67%) is higher than that of the control group (75.56%). The difference has statistical significance ( $P < 0.05$ ). See Table 6.

**Table 1**

PLT comparison between the two groups before and after the treatment ( $\times 10^9/L$ ,  $x \pm s$ ).

Group	PLT before the treatment	PLT after the treatment	P
Observation group (n = 48)	24.14 $\pm$ 2.98	114.17 $\pm$ 13.26	<0.05
Control group (n = 45)	23.90 $\pm$ 3.02	91.18 $\pm$ 8.87	<0.05
P	>0.05	<0.05	

**Table 2**

The comparison between the two groups about the time that PLT reaches normal and peak values, and PLT peak values.

Group	Time for PLT to reach normal value (d)	Time for PLT to reach peak value	PLT peak value ( $\times 10^9/L$ )
Observation group (n = 48)	6.93 $\pm$ 1.04	9.37 $\pm$ 0.99	326.16 $\pm$ 32.77
Control group (n = 45)	10.07 $\pm$ 1.34	13.86 $\pm$ 1.35	180.24 $\pm$ 17.24
P	<0.05	<0.05	<0.05

Note: Compared with the control group, \* $P < 0.05$ ; compared with that before the treatment, # $P < 0.05$

### 3.7. The comparison of the incidence rate of adverse events

After the treatment, 2 patients in the control group have dizziness or headache, 3 liver function abnormality, and the incidence rate of adverse events 11.11% (5/45); 1 in the observation group

have dizziness or headache, 1 liver function abnormality, and the incidence rate of adverse events 4.17% (2/48). The difference between the group has statistical significance ( $\chi^2 = 3.890$ ,  $P < 0.05$ ).

## 4. Discussion

As a common hemorrhagic disease, ITP is considered to be a disease related to the immune system, which can be divided into acute and chronic types (Portielje et al., 2001; Tarantino, 2000). Children tend to contract acute ITP, male and female share a similar incidence rate. The chronic type is commonly seen among young females, while the acute type symptomizes serious hemorrhage, which presents self-limited features, recovers or cures after weeks' active therapy. A small number of patients whose symptoms will protract to about half a year, and some develop into the chronic type, whose hemorrhage is not that serious but it happens repeatedly and lasts long. After diagnosis and treatment, patients can recover or at least relieve (Bourgeois et al., 2003; Mcmillan and Durette, 2004). The aim to treat the disease is to control the hemorrhage, reduce the damage to blood platelet. However, it is not advised to increase PLT amount to the normal level, so as to make sure patients are free from dangers caused by hemorrhage and great adverse reaction out of over-treatment. Glucocorticoid should be adopted for the first treatment, while those under grave conditions can use a large amount of gamma globulin. Rh(D) immune globulin is also used for treatment in other countries. Besides, splenectomy can also be adopted (McMillan, 1997).

**Table 3**

The comparison between the two groups about the changing situation of inflammatory factors ( $x \pm s$ ).

Group	TNF- $\alpha$ (pmol/ml)		IL-6 (pg/ml)	
	Before the treatment	After the treatment	Before the treatment	After the treatment
Observation group (n = 48)	161.41 $\pm$ 18.60	65.52 $\pm$ 8.35**	88.78 $\pm$ 10.30	36.36 $\pm$ 3.94**
Control group (n = 45)	163.16 $\pm$ 15.48	100.56 $\pm$ 12.62#	89.04 $\pm$ 9.42	55.78 $\pm$ 7.03#

Note: Compared with the control group, \* $P < 0.05$ ; compared with that before the treatment, # $P < 0.05$

**Table 4**

The level change of peripheral blood T lymphocyte in both groups before and after the treatment (% ,  $x \pm s$ ).

Group	CD3 <sup>+</sup>	CD3 <sup>+</sup> CD95L <sup>+</sup>	CD3 <sup>+</sup> Caspase-3 <sup>+</sup>	CD3 <sup>+</sup> Caspase-8 <sup>+</sup>
Observation group (n = 48)	62.4 $\pm$ 10.2	5.6 $\pm$ 3.9	4.5 $\pm$ 3.6	4.9 $\pm$ 3.6
Control group (n = 45)	69.1 $\pm$ 5.0	8.4 $\pm$ 8.1	3.0 $\pm$ 2.5	9.1 $\pm$ 6.4
t	4.191	2.150	2.479	4.063
P	<0.01	0.034	0.015	<0.01

**Table 5**

The level change of peripheral NK cell in both groups before and after the treatment (% ,  $x \pm s$ ).

Group	NK <sup>+</sup>	NK <sup>+</sup> CD95L <sup>+</sup>	NK <sup>+</sup> Caspase-3 <sup>+</sup>	NK <sup>+</sup> Caspase-8 <sup>+</sup>
Observation group (n = 48)	62.4 $\pm$ 10.2	5.6 $\pm$ 3.9	4.5 $\pm$ 3.6	4.9 $\pm$ 3.6
Control group (n = 45)	69.1 $\pm$ 5.0	8.4 $\pm$ 8.1	3.0 $\pm$ 2.5	9.1 $\pm$ 6.4
t	4.191	2.150	2.479	4.063
P	<0.01	0.034	0.015	<0.01

**Table 6**

The comparison of curative effect between the two groups [case (%)].

Group	Slightly effective	Effective	Ineffective	Total effective rate
Observation group (n = 48)	27(56.25)	17(35.42)	4(8.33)	44(91.67)
Control group (n = 45)	17(37.78)	17(37.78)	11(24.44)	34(75.56)
Z				-2.619
P				0.007

Glucocorticoid is a steroid hormone secreted by epinephrine cortex, which can also be artificially synthesized. It can inhibit macrophagocyte from phagocytosing and processing antigen, so as to accelerate the damage and breakdown of lymphocyte and reduce the amount of lymphocyte in circulation by excluding broken ones out of the vessel. Therefore, glucocorticoid has an immunosuppressive function. In addition, it can also strengthen the resistance of capillaries, reduce its permeability, inhibit the formation of blood platelet antibody, so it is chosen to serve the initial therapy for ITP. However, many researches suggest that the curative effect is not ideal for some patients who have undergone glucocorticoid treatment, which even produces side effects after being taken for a long time (Allison and Eugui, 2000; Filler et al., 2003; Riskalla et al., 2003). In view of this, many researches targeting ITP have been conducted adopting glucocorticoid in combination with immunosuppressor, which yields great curative effect. MMF, as an immunosuppressor, is the derivative of mycophenolic acid, which can specifically inhibit the activity of 1MODH from de novo synthesis of lymphocyte purine, so as to inhibit the proliferation of lymphocytes. As for ITP treatment, MMF serves to reduce blood platelet lesion by inhibiting the formation of lymphocytes and further reduce autoimmune lesion by inhibiting antibody formation, thus yielding great clinical effect (Howard et al., 2002). Therefore, MMF is widely accepted by patients and medical staff as a new type of specific medicine for ITP treatment.

But patients tend to be infectious out of the immunosuppression of MMF; though its hepatotoxicity and nephrotoxicity are not reported, a small number of patients will have a transient increase of liver enzymes; adverse reaction and even gastrointestinal tract reaction, bone marrow inhibition and tumor. In the research, 3 patients in the control group have liver function abnormality, which has something to do with the toxic and side effect of the medication. Therefore, it has become a hotspot issue on how to combine medicines when it comes to increase the curative effect and reduce adverse events (Ciancio et al., 2003; Johnson et al., 2000).

In the research, the curative effect of the observation group is superior to that of the control group. After the treatment, the PLT amount in both groups increase, and the value of the observation group is higher than another one. The difference has statistical significance ( $P < 0.05$ ); the time for PLT amount to reach normal and peak values for the control group is longer than that of another one, the observation group is higher than that of another one as regards PLT peak value. The difference has statistical significance ( $P < 0.05$ ). The incidence rate of adverse events in the observation group is lower than that of another one. The difference has statistical significance ( $P < 0.05$ ). It is safe and clinically meaningful to treat ITP with Prednisone and Mycophenolate. Multiple inflammatory factors serve to adjust immunofunctions and activate immunocytes in the occurrence and development of ITP. The researches suggest that inflammatory factors like TNF- $\alpha$  and IL-6 in patients with ITP are abnormally high. As the inflammatory factor with double biological activity, TNF- $\alpha$  is secreted by the mononuclear macrophage. Multiple inflammatory factors and large amounts of TNF- $\alpha$  can lead to the imbalance of immune function. B lymphocytes, T lymphocytes and mononuclear macrophages can secrete IL-6, multifunctional inflammatory cytokines, which can activate natural killer cells (NK cells), T lymphocytes, B lymphocytes and secrete antibodies (Saleh et al., 2000). It is showed in the research result that before the treatment, the difference concerning the level of TNF- $\alpha$  and IL-6 between the two groups has no statistical significance ( $P > 0.05$ ), while after the treatment, the level of TNF- $\alpha$  and IL-6 is lower, and the level of the observation group is lower than that of another one. The difference between and within the group has statistical significance ( $P < 0.05$ ). Therefore,

Prednisone in combination with Mycophenolate can effectively lower the level of TNF- $\alpha$  and IL-6.

It is found that patients with ITP are different in Caspase-3 and Caspase-8 after the treatment. Caspase-3 is a key protease, whose amount has been lowered after the treatment, and it shares a consistency with ITP patients treated with Prednisone, which can effectively control the disease (Zaja et al., 2003). When it comes to the curative effect on patients, the result shows that Caspase-3 can rapidly reflect the FasL on the surface layer of T cells and NK cells and effectively recognize the Fas on relevant target cells, produce the compound of Fas/FasL through the combination of noncovalent bonds and convey the signal of cell apoptosis to target cells after the reaction (Giagounidis et al., 2002). It is also found that CD3<sup>+</sup>Caspase-8<sup>+</sup> is positively correlated with NK<sup>+</sup>Caspase-8<sup>+</sup> ( $P < 0.05$ ), which means T lymphocytes, in its process of apoptosis, is related to NK cells (Stasi et al., 2001). Besides, NK cells are negatively correlated with CD3<sup>+</sup> ( $P < 0.05$ ), which may be caused by immune function abnormality of patients with ITP for the first time. NK<sup>+</sup>Caspase-8<sup>+</sup> is positively correlated with NK<sup>+</sup> CD95L<sup>+</sup>, but the difference has no statistical significance ( $P > 0.05$ ). NK<sup>+</sup>Caspase-3<sup>+</sup> is positively correlated with NK<sup>+</sup> CD95L<sup>+</sup> ( $P < 0.05$ ), which indicates Caspase-3 and Fas/FasL on NK cells has something to do with cell apoptosis. It is found that T lymphocytes exist in the pathogenesis of patients with ITP, Fas/FasL system shares a connection with the apoptosis process of Caspase protease, while NK cells exist in the Caspase apoptosis process (Cooper et al., 2004).

## 5. Conclusion

Above all, the curative effect of Prednisone in combination with Mycophenolate on ITP patients is better than orally taking Prednisone tablets. Moreover, when it comes to Prednisone in combination with Mycophenolate, both the PLT amount and immunocompetence are improved without much adverse reaction. And the molecules of peripheral blood T lymphocyte and NK lymphocyte can be effectively adjusted to relieve the symptoms, which is trustworthy to be popularized for clinical practices.

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