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Evaluating the Treatment Indices of Immunologic Thrombocytopenic Purpura in Pediatric Patients

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Abstract

Background: Immunologic Thrombocytopenic Purpura (ITP) is considered as one of the common diseases among children. The aim of this study is evaluating the treatment indices of ITP in pediatric patients.

Materials and Methods: In this observational follow-up study, 123 ITP patients were assessed in term of medical history, physical examination, and laboratory tests based on the type of treatment.

Results: Among 123 ITP patients, 70 (56.9%) were female and 53 (43.1%) were male with mean age of 4 years. Considering the platelet count of > 20,000, 115 (93.6%), 4 (3.3%) were treated in less than a month (acute) and 1-6 months (sub-acute). Thirty two patients (26%) did not reach the normal platelet count in 6 months (chronic). IVG, steroid, RhoGAM, steroid+ IVIG, RhoGAM + IVIG, RhoGAM+steroid+IVIG therapy was done in 10.6, 15.4, 2.4, 41.5, 4.1, and 26, respectively. Three patients did not receive any medication. There was no significant relationship between the onset of clinical symptoms and the onset of treatment based on 20,000 platelet count; however, regarding the platelet count of 150000, the relationship was statistically significant. The frequency of ITP was higher in females. There was no report on Intra-cerebral hemorrhage (ICH). In addition, 11 patients (8.9%) were provided with splenectomy. The treatment with combinational therapy of RhoGAM and IVIG was regarded as the highest treatment rate. In addition, the highest length of hospotalization based on initial treatment belonged to steroid treatment followed by the combinational therapy of steroid and IVIG. The patients receiving IVIG were the ones with the highest cost for the first 24 hours of treatment, and regarding the later hospitalization, the patients treated with steroid and combinational therapy of steroid+IVIG had to pay the highest medical expenses.

Conclusion: No significant relationship between the symptoms, platelet count, and the type of treatment.

Keywords: Chronic, Immunologic Thrombocytopenic Purpura, Medical Costs, Prognosis, Treatment Process.

Introduction

Immunologic Thrombocytopenic Purpura (ITP) is a childhood acquisitive thrombocytopenia, which is an undetected benignant disorder (1, 2). This is the most common disease that acutely reduces the platelet count in the children who are actually considered to be healthy. In most cases, one to four weeks after being affected by a prevalent viral infection, an autoantibody is created against the platelet level which causes a sudden reduction in platelets. This disease might be revealed through some mild symptoms such as petechiae, purpura, and ecchymosis on the skin to some severe ones like severe menorrhagia, Intra-cerebral Hemorrhage (ICH), or severe bleeding that requires emergency procedures (3-5). Seventy to eighty percent of the patients will observe automatic recovery in six months, and it seems that the treatment does not have any effect on the normal course the disease. There is also a view that the early treatment results in an increase in the platelet count to over 20000 and prevents the rare yet dangerous case of ICH (6).

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Several treatments have been proposed on this disease, and various studies have reported different effects; these treatments include medication (prednisolone, RhoGam, and IVIG) and surgical (splenectomy) ones. Very few studies have been conducted on the common treatment costs of this disease. Moreover, many studies have been conducted in recent decades on the prevalence, diagnosis, and treatment of ITP, but there is still room for further exploration and identification of its predictive factors. Various studies have proposed the old age, female gender, and silent onset as predisposing factors for chronic form of this disease (6, 7). Therefore, the present study aims at investigating the ITP cases, in terms of treatment process, taken treatments, and treatment costs of the patients who are lower than 14 years old and refer to Sadouqhi Hospital in Yazd, Iran.

Materials and Methods

The present observational follow-up study was conducted on 123 children (average of 4 y/o) hospitalized with ITP during 2011-16. The clinical findings and test results of these patients were extracted from their medical files. The required data were collected at Shahid Sadoughi Hospital in Yazd. In order to get to the intended data, first of all, the patients' info including biography, physical examination, and necessary tests (CBC, immunologic and virologic tests) were gathered. Then, the type of treatment was determined according to the clinical symptoms, tests, and platelet counts. After that the patients were proposed to the treatment. CBC tests were carried out with two days, one-month, and six-month intervals, and the results were interpreted according to the patient's response to the treatment process. Besides, in this study, the average costs of treatment were also determined. The input criteria of the study were as follows:

1) Patient's clinical symptoms: The presence of purpura, normality of other clinical examinations showing the absence of lymphadenopathy and hepatosplenomegaly
2) Reduced number of platelets in platelet count and blood smear, but no abnormality in Hemoglobin(Hb) and White Blood Cells(WBC)
3) Increased or normal mega karyocytes in bone marrow aspiration and no change in myeloid and erytroid series.
4) Rejection of the secondary causes of thrombocytopenia including hypersplenism, DIC(Disseminated intra vascular coagulopathy), systemic lupus, and medication

Besides, the output criteria of the study were the followings:

1- aged less than six months and more than 14 years old
2- lack of the necessary diagnostic criteria for ITP
3- Insufficient data in the patient's record
4- Patient's failure to continue the treatment (due to the reasons such as moving to another city).

Results

In the present study, 123 children were examined. The subjects were aged from six months to 14 years old. Considering gender, there were 53(43.1%) male and 70 (56.9%) female subjects performing in this study. Moreover, ITP was more frequent in females (56.9%). In addition, the frequency of splenectomy was 8.9%.

The patients were divided into acute and chronic groups according to their achievement of normal platelet count in six months. Frequency distribution of ITP patients' response to the treatment regarding the platelet count (20,000) was shown in Table I. Based on results, 115 (93.6%) patients had reached the platelet count of higher than 20,000 within one

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month (responding to the treatment), in four patients (3.3%) between one and six months (subacute), and four patients (3.3%) reached this level of platelet in six months. Frequency distribution of normalized platelet count in ITP patients regarding the platelet count (150000) in Table II. There were also four patients (3.3%) who reached this level of platelet after six months. Within six months, the platelet count reached over 150,000 in 91 (74%) out of 123 patients, but it failed to exceed 150,000 in 32 (26%) patients (chronic ITP).

Frequency distribution of ITP patients treated with RhoGam, steroid, and IVIG based on platelet count of less than 20,000 was summarized in Table III. Considering the response to the treatment (platelet count of over 20,000) in the first month of hospitalization, 13 (11.3%), 16 (13.9%), and 2 (1.7%) patients were treated with IVIG, steroid, and RhoGam, respectively.

Furthermore, considering the combinatory treatments, 49 (42.6%) patients received IVIG and steroid, 5 (4.3%) received IVIG and RhoGam, one (0.9%) received steroid and RhoGam, and 26 (22.6%) received IVIG, RhoGam, and steroid. Moreover, three patients received no medication at all.

Considering the achievement of normal platelet count (over 150,000) in the first month of hospitalization, 10 (14.5%) patients were treated with IVIG, 10 (14.5%) patients were treated with steroid, and two (2.9%) patients were treated with RhoGam. Also, 39 (56.5%) patients were treated with IVIG and steroid, two (2.9%) with IVIG and RhoGam, and five (7.2%) patients were treated with IVIG, RhoGam, and steroid. It is worth mentioning that no patient received steroid and RhoGam treatment, and three (2.5%) patients received no medication.

The combinatory treatment style of IVIG and steroid was the most applied medical treatment regarding the patients' response to the treatment (platelet over 20,000) and the type of primary treatment in the first 24 and 48 hours. The mean frequency of admission was higher in the patients treated with RhoGam and IVIG method compared with the ones provided with other types of treatments (MD=1, Mean=7.4), and the highest median of hospitalization was observed in patients treated with the combinatory method of RhoGam, IVIG and steroid (MD=3, Mean=4.25).

Considering the average duration of hospitalization, based on the type of primary treatment, in the first admission, the RhoGam and steroid method with a mean of MD=9 demonstrated the highest duration. Also, RhoGam and IVIG method showed the next long duration in the first admission MD=7 (Table IV).

The highest treatment cost in the first 24 hours belonged to the patients receiving IVIG, and the ones treated with steroid and IVIG paid the most in the next 48 hours.

Regarding the patients' response to the treatment (platelet over 20,000) and the time interval between the clinical symptoms and the onset of the treatment, 81 patients were treated in less than one week (P=0.96) (Table V).

Based on normalization of platelet count (over 150,000) and the time interval between the clinical symptoms and the onset of the treatment, 52 patients were provided with the treatment in less than one week (P=0.015) (Table VI).

Table I: Frequency distribution of ITP patients' response to the treatment regarding the platelet count (20,000)

Platelet count	Frequency	Percentage
Over 20,000 in one month	115	93.5
Over 20,000 from 1 to 6 months	4	3.3

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Over 20,000 after six months	4	3.3
Total	123	100

Table II: Frequency distribution of normalized platelet count in ITP patients regarding the platelet count (150000)

Platelet count	Frequency	Percentage
Over 150,000 in one month	69	56.6
Over 150,000 from 1 to 6 months	22	17.9
Under 150,000 after six months	32	26
Total	123	100

Table III: Frequency distribution of ITP patients treated with RhoGam, steroid, and IVIG based on platelet count of less than 20,000

Medication/platelet count	IVIG	Steroid	RhoGam	Steroid + IVIG	RhoGam + IVIG	Steroid + RhoGam	IVIG + RhoGam + steroid	No medication	Total number of patients
Over 20,000 in one month	13 11.3 %	16 13.9%	2 1.7%	49 42.6%	5 4.3%	1 0.9%	26 22.6%	3 2.5%	115 100%
Over 20,000 in 1 to 6 months	0 0%	0 0%	0 0%	2 50%	0 0%	0 0%	2 50%	0 0%	4
Over 20,000 after six months	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	4	0 0%	4

Table IV: Frequency distribution of platelet count normalization outcome in ITP patients based on primary treatment (in the first 48 hours)

Platelet count/treatment	Over 150,000 in one month	Over 150,000 in 1 to 6 months	Under 150,000 after 6 months	Total
IVIG	20 69%	6 20.7%	3 10.3%	29 100%
Steroid	17 51.5%	5 15.2%	11 33.3%	33 100%
RhoGam	3 75%	0 0%	1 25%	4 100%
IVIG + Steroid	28 57.1%	10 25.4%	11 22.4%	49 100%
IVIG + RhoGam	0 0%	1 25%	3 75%	4 100%
Steroid + RhoGam	-	-	-	-
Steroid + RhoGam + IVIG	1 100%	0 0%	0 0%	1 100%
Total	69 56.1%	22 17.9%	32 26%	123 100%

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Table V: Frequency distribution of the patients' response to the treatment based on the time interval between clinical symptoms and onset of treatment

Platelet count/interval between symptoms and treatment	Over 20,000 in one month	Over 20,000 in 1 to 6 months	Over 20,000 after 6 months	Total	P value
Under one week	81 93.1%	3 3.4%	3 3.4%	87 100%	0.96
Over one week	34 94.4%	1 2.8%	1 2.8%	36 100%	
	115 93.5%	4 3.3%	4 3.3%	123 100%	

TableVI: Frequency distribution of platelet count normalization based on the time interval between clinical symptoms and onset of treatment

Platelet count/interval between symptoms and treatment	Over 150,000 in one month	Over 150,000 in 1 to 6 months	Over 150,000 after 6 months	Total	P value
Under one week	52 59.8%	10 11.5%	25 28.7%	87 100%	0.015
Over one week	17 47.2%	12 33.3%	7 19.4%	36 100%	
	69 59.1%	22 17.9%	32 26%	123 100%	

Discussion

Several studies have been conducted on the prevalence, diagnosis, and treatment of ITP in recent decades, but there is still room for more questions and identification of predictive factors (8-10).

Since ITP is one of the common diseases of otherwise healthy children, and due to the fact that the variety of views on its treatment, as a report, the present study can help provide information for further studies. These studies can help in identifying the effect of the type and timing of treatment on the progression of the disease and having some changes in the outcome of ITP patients. Furthermore, the costs of various treatment methods are also extracted. In a prospective study conducted by Rosthoj et al. in five European countries between 1998 and 2000, 501 children suffering from ITP who had referred to the medical centers were studied in six months (11). This study aimed at determining the risk period in children with platelet count of less than 20000/dl, and also recording the frequency of their bleeding. Out of the 501 children, 409 were studied over six months. Fifty

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eight percent of the patients suffered from petechiae and purpura bleeding, 38% of them had mucosal hemorrhage, and 3% required blood transfusion. Chronic ITP was observed more among the 6 to 14 year-old girls. In that study, no ICH cases were reported. The findings of the above-mentioned study revealed that most of ITP patients are at risk of severe hemorrhage in the first month of the disease, the continuation of severe thrombocytopenia is not that much important. In an overview conducted by Sezgin et al., in Turkey, some ITP patients were studied from 2000 to 2009, and their records were explored according to the International Working Group (IWG) definitions (12). A total of 201 children were studied from 12 to 131 months. The age mean of the patients was 69 months (7 to 208 months), and the mean platelet count was estimated to be 19000/dl (ranging from 1000/dl to 93000/dl), in that study.

Petechiae and ecchymosis was considered to be the most common symptoms (71%) in this disease. Thirty six children (18%) had been admitted with nasal or gum hemorrhage associated with petechiae and ecchymosis. 23 (11%) had no bleeding. IVIG was proposed to 66 (65%) children, and corticosteroid was chosen as the primary treatment for 36 (35%) children. The patients' response to the treatment was the same in both kinds of medications ($P>0.05$).

On the other hand, two risk factors were identified for chronic ITP, including the female gender and the age being over ten year-old. Life-threatening bleeding occurred in 9 (5%) patients, and 7 (3%) patients were provided with splenectomy. According to the final results, the female gender and the age of over ten years can be considered as the two important factors for long-term follow-up of the ITP patients.

The present study was conducted on 123 ITP patients being aged from 6 months to 14 years old. Regarding the platelet count of over 20 thousand (responding to the treatment), in the first month of illness, the dry symptoms (petechiae, purpura, and ecchymosis) were observed in 104 (90.4%) patients and wet symptoms (epistaxis, hematuria, and mucosal hemorrhage) were found in 42 (36.5%) patients.

Considering the platelet count of over 150 thousand (responding to the treatment), in the first month of illness, the dry symptoms (petechiae, purpura, and ecchymosis) were observed in 62 (89.9%) patients and wet symptoms (epistaxis, hematuria, and mucosal hemorrhage) were found in 24 (34.5%) patients. There was no significant relationship between clinical symptoms and platelet count in the first month in either group. The frequency of chronic ITP was more in the female gender, and no cases of life-threatening hemorrhage for example Intra cranial hemorrhage (ICH) were reported, but 11 (8.9%) cases of splenectomy were reported. Based on the patients' response to the treatment (over 20000 platelet count) and the type of primary treatment in the first 24 hours, the combinatory treatment of IVIG and steroid was the most frequent type of treatment. There was no significant relationship between the patients' response to the treatment and the type of primary treatment. Besides, regarding the normalization of platelet count (over 150 thousand) and the type of primary treatment in the first 24 hours, IVIG and steroid was the most frequent type of treatment. There was a significant relationship between normalization of platelet count and the type of primary treatment.

In a study conducted by Treutiger et al. on 506 ITP patients, in 98 medical centers of five European countries between 1998 and 2000, the effect of early treatment with IVIG or corticosteroids on reducing the side effects of the disease was explored (13). Out of 506 children, only 287 were

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treated in the first 14 days after the diagnosis, and the medical centers were divided into three groups accordingly. The course of the disease was investigated from 15 days to six months after the diagnosis and treatment. The study was concerned with the children who were suffering from the platelet count of less than 20000/dl, and the exploration kept on going until the achievement of a platelet count of over 150 thousand/dl.

The final conclusion showed no difference in the recovery rate a month after diagnosis. In the explored three groups, the chronic ITP was reported to be 27%, 22%, and 25%, respectively. The results showed that the treatment programs can accelerate the raise in the platelet count of children suffering from acute ITP, but it cannot prevent its progress toward chronic ITP, or reduce its mortality rate during the follow-up process.

In the present study, the treatment process of ITP patients was studied over six months. In a one month period, 115 (93.5%) patients reached the platelet count of over 20 thousand, and 69 (56.6%) reached the platelet count of 150 thousand. As the ITP patients were explored in the present study, there was no significant relationship between the onset of clinical symptoms and initiation of treatment considering the platelet count of 20000 (the response to the treatment), but there was a significant relationship between these two variables considering the platelet count of 150 thousand (normalization of the platelet count). In fact, if the platelet count of over 20000 is regarded as treated, the results of the present study also suggest that earlier treatment has no effect on chronicity, but earlier treatment will be effective, if normalization of the platelet count is taken as the criterion.

In a study conducted by Ramyar et al. on 202 hospitalized patients receiving the treatment, in Tehran pediatric center, the medical effects of IVIG and prednisolone were compared (14). According to this study, there was no significant difference between the medical effects of these two medicines. ITP was more frequent among the male gender. They concluded that there was no significant difference between the effects of IVIG and prednisolone. In this study, prednisolone was recommended as the treatment of ITP, given its availability and inexpensiveness.

In the current study on the ITP patients, in the first 24 hours, 37 patients were treated with steroid alone and 29 patients with IVIG alone. Ultimately, no significant difference (including the chronicity of the disease) was observed between these two methods. However, considering other treatment methods used in this study, there was a significant relationship only in combinatory treatment (IVIG, steroid and RhoGam), regarding the platelet count of 20000 and 150000. Unlike the results of the above-mentioned study, in the present study, the frequency distributions of acute and chronic ITP were higher in the female gender.

In the study conducted by Treutiger et al., the disease period was explored from 15 days to six months after the diagnosis and treatment. This research work was just concerned with the children with the platelet count of less than 20000/dl, and the exploration continued until the platelet count reached over 150 thousand/dl (15). The final conclusion revealed no difference in recovery rate one month after the diagnosis. On the other hand, in the present study, out of 123 patients, 115 (93.4%) ones had the platelet count of over 20.000, after one month.

Besides, a review paper was developed by Lamiae Grimaldi et al., in France, from 2008 to 2013, on 257 children (6 to 18 year-old) suffering from ITP (16). The patients' data were collected in 12 months. The results showed that out of 211 (80%)

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available patients, 160 (76%) ones had fully recovered in one year, and 51 (24%) were suffering from chronic ITP. In their study, 80% of the patients were proposed to the treatment, of whom, 26 (30%) were treated with steroid, 99 (47%) with IVIG, 46 (22%) with steroid and IVIG, and two (1%) patients received platelets. The results showed that the mucosal hemorrhage and platelet count were effective in the physician's decision on the initiation of the treatment. In that study, the chronicity was more observed in the girls over ten years of age and the ones with the platelet count of over 10000.

In the present study, out of the 123 patients, 91 (74%) patients reached the platelet count of over 150 thousand after six months; however, 32 (26%) did not reach this level of platelet count (Chronic ITP). It is worth mentioning that three patients received no medication, but considering the remaining patients, 13 (10.6%) received IVIG, 16 (13%) steroid, 2 (1.6%) RhoGam, 51 (41.5%) steroid plus IVIG, 5 (4.1%) RhoGam plus IVIG, 1 (0.8%) steroid plus RhoGam, and 32 (26%) combination of the three. The only significant relationship was observed between the platelet count and the type of combinatory treatment (in the first 48 hours). But due to the fact that only one patient had received all three medications; the result cannot be scientifically generalized.

In a study conducted by Celik et al. which was concerned with the comparison of ITP treatments, ITP patients were randomly divided into three groups (17). One of these groups received RhoGam, the other group was proposed to methyl prednisolone, and the patients of the last one were treated by IVIG. There was no significant difference between three groups regarding the platelet count in the first three days. Seven days after the treatment, the platelet count was the lowest in the group receiving methyl-prednisolone, and the RhoGam group revealed the lowest hemoglobin level. The chronicity was 30% in RhoGam group, 25% in methyl-prednisolone, and 25% in IVIG group. However, these differences were not statistically significant which can be in line with the findings of the present study.

In a study conducted by Brien et al. (2007), in Thailand, entitled "Cost and benefit of the treatment of ITP patients", ITP patients were studied and treated according to the platelet count of less than 20000 (18). The patients were provided with four treatment strategies, including

1) 0.8gr/kg dose of IVIG
2) 75µgr/kg dose of RhoGam
3) 30mgr/kg dose of prednisolone for three days
4) 4mgr/kg dose of prednisone for 4 days

Then, the costs of treatment with these four methods were determined. The total cost of treating a 20kg-waighted child was as follows: prednisone $786, methylprednisolone $1346, RhoGam $2035, and IVIG $2492. Compared with RhoGam and prednisone, the treatment strategies with IVIG and methylprednisolone were the most expensive and the least effective, respectively. Although the platelet count increased faster with RhoGam treatment, it was more expensive than prednisone. But, the clinical benefits of RhoGam justify its cost. Moreover, using high doses of prednisone over shorter periods is an effective and cheaper treatment option for patients suffering from acute ITP.

In a review paper developed by Hord et al. from 1986 to 1999, in France, 126 ITP patients with the platelet count of less than 20000 who were admitted over a five-year period, were surveyed (19). The efficacies of IVIG and steroid were assessed, resulting in the following findings: the patients' age average was five years and the average platelet count was 6600. 69

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patients were male and 57 were female. 63 patients were treated with steroid and 17 were proposed to IVIG. The treatment selection was done according to the physician's preference, and no specific treatment was administered for patients with mild or severe hemorrhage.

Ultimately, there was no significant difference between IVIG and steroid. Moreover, the hospitalization period of both groups were compared. The patients of IVIG group were hospitalized for 3 days and the ones treated with steroid spent 2.9 days in the hospital. The average hospitalization cost was $4942 for IVIG patients and $1452 for the ones receiving steroid. The observed difference, in this case, was statistically significant.

In the present study, RhoGam and IVIG treatment had the highest range of admission. Besides, the longest hospitalization, in the primary treatment, was observed in steroid treatment, followed by steroid plus IVIG.

Moreover, the highest cost for the first 24 hour of treatment belonged to the ones receiving IVIG, and to steroid recipients in further admissions. The patients proposed to the combinatory treatment of steroid plus IVIG were at the next level.

Conclusion

In the present study, there was no significant relationship between symptoms, platelet count and the type of treatment. The frequency of splenectomy was 8.9%. The acute and chronic types of ITP were more frequent among the female gender. The combinatory treatment with steroid and IVIG was considered to be the most frequently used primary treatment based on the platelet count (20000 and 150000). Moreover, the highest cost of the first 24 hours of treatment was paid by the ones receiving IVIG, and the ones receiving steroid and steroid plus IVIG had to pay the highest in further admissions. Data showed that the patients who do not receive the treatment on the onset of the symptoms in the first week have less chance for normalization of the platelet count or greater chance for chronicity of ITP. This should be seriously taken into account, especially, in female patients.

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Author contributions

Mahdieh Saberi: Data collection and article writing. Mehrdad Shekiba: Data collection and articlr writing, Alireza Jenabzade: management of study and article writing, Hadi Zare-Zardini: Data assessment and article writing

Conflict of interest

The authors declare no conflict of interest.

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