Idiopathic Autoimmune Thrombocytopenic Purpura (ITP) in adult; review of 50 cases admitted to Baghdad teaching hospital

Adil S. Al-Aqabi* **CABM, FICM (hem)**
Alaa F. Alwan** **FICM (med), FICM (hem)**

Summary:

Background: Idiopathic autoimmune thrombocytopenia purpura (ITP) is an isolated thrombocytopenia in a patient with no clinically apparent associated conditions or factors that can cause thrombocytopenia. The syndrome of ITP is caused by platelet-specific auto-antibodies that bind to autologous platelets. The diagnosis of ITP is usually a diagnosis of exclusion based on a demonstration of peripheral thrombocytopenia. Steroids are the conventional first-line therapy for adult ITP. Most patients demonstrate a response to steroids within 2 to 4 weeks, but a late response is possible.

Patients and Methods: A prospective study on 50 patients with diagnosis consistent with ITP, initially treated by steroid, patients who were non responders to steroids or relapsed following its withdrawal offered splenectomy

Results: Ten patients (20 %) had permanent satisfactory remission following steroid therapy, while other 40 patients (80 %) were either non responders (20 patients, 40 %) or relapsed (20 patients, 40%). Twenty patients (40%) underwent splenectomy, all of them initially responded, after 3-6 months, 17 patients of them (85%) were still in complete remission, while 3 patients (15%) were refractory ITP and required further treatment.

Conclusion: Steroid therapy is less effective in achieving satisfactory remission in adult patient with ITP; on the other hand, splenectomy had more sustained response after steroid failure.

Keywords: ITP: idiopathic autoimmune thrombocytopenia purpura.

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Introduction:-

Adult idiopathic thrombocytopenic purpura (ITP) is a chronic acquired organ-specific autoimmune hemorrhagic disease. The thrombocytopenia of ITP is mainly attributed to the early destruction of platelets by the activated reticuloendothelial system, following their sensitization by antiplatelets glycoprotein auto antibodies(1).The reported prevalence of ITP is l-13 per 100 000(2). It is more common than alloimmune thrombocytopenia and autoimmune hemolytic anemia (3); it is more common in females than males (4). In 1982, van Leeuwen first identified platelet membrane glycoprotein IIb/IIIa as a dominant antigen by demonstrating that the auto antibodies eluted from ITP platelets bound to normal platelets but not to platelets from patients with Glanzmann thrombasthenia (5), gpIIb/IIIa and gpIb/V/IX are the major platelet antigens. Serum auto antibodies can react with IIb or IIIa or the intact IIb/IIIa complex. (6). Auto antibodies bind to platelets and cause thrombocytopenia primarily by shortening platelet survival. However, auto antibodies have also been reported that bind to glycoproteins and activate platelets (7). Platelets survival, measured using ^{51}chromium- or ^{111}indium-labeled platelets, is shortened in ITP, and the survival time can range from 2 to 3 days to a matter of minutes (8).

**consultant hematologist /Baghdad Teaching Hospital/Medical City*
***Assistant professor / the National Center of Hematology/ Almustansiriya University*

Bleeding after trauma without spontaneous hemorrhage is usual in mildly affected patients with platelet counts >50,000/µl. Thrombocytopenia associated with counts between 10,000 and 50,000/µl results in spontaneous hemorrhagic manifestations of varying severity, such as ecchymoses and petechiae. Patients with platelet counts <10,000/µl are at risk for serious morbidity and mortality from bleeding, although the mortality rate is actually quite low. Patients who have an increased risk of bleeding include those with a history of bleeding, those with additional bleeding diatheses, and patients >60 years of age (9). Autoimmune thrombocytopenia is a diagnosis of exclusion and relies on clinical impression. A number of different types of antiplatelets antibody tests have been developed and reported through the years (10) , none of these tests is in routine clinical use, and experts disagree on their role in the diagnosis of ITP. Future direction might include the use of flow cytometry in the diagnosis and follow-up of autoimmune thrombocytopenia (11).Steroids are the conventional first-line therapy for adult ITP. Spontaneous remissions are very uncommon in adults, with an estimated occurrence of <5%. Most patients demonstrate a response to steroids within 2 to 4 weeks, but a late response have been described after 6 months in a small number of patients (12) . Complete and partial responses in patients treated with prednisone (usually, 1 mg/kg/day as starting dose) occur in about 65 to 85%, but sustained responses after discontinuation of the drug occur in

only 25% or less of patients. Platelet counts usually increase within 1 week in responding patients and have usually reached peak values by 2 to 4 weeks. Patients who have not had any response by 4 weeks are unlikely to respond to prednisone and therefore should be considered for splenectomy or other forms of treatment. No pretreatment patient characteristics have predicted a patient's response to steroids.(2,8) Patients with severe thrombocytopenia (<10,000/µl) who do not respond to steroids (administered for up to 4 to 6 weeks) or who relapse during steroid tapering, and patients with platelet counts of <30,000/µl for periods up to 3 months, should be considered for splenectomy (12). Sustained complete responses to splenectomy (variously defined as platelet counts of 100,000 to 150,000/µl) have been reported in about 50 to 80% of patients, depending on the series. After the operation, the platelet count may increase rapidly, often within 24 to 48 hours, Patients who do not respond to splenectomy or who relapse after an initial response to splenectomy should be studied for the presence of accessory spleens (13). No randomized controlled trials have reported treatment options for patients who do not respond to treatment with both steroids and splenectomy. Patients who are asymptomatic and have platelet counts between 30,000 and 50,000/µl may be managed with careful observation. Symptomatic patients with platelet counts <30,000/µl who had an initial response to steroids can be retreated with prednisone and then tapered to find the minimum dose that can maintain the patient hemorrhage-free, even if the platelet count is not >30,000/µl (14). Additional therapies that have been beneficial in some patients with refractory ITP are long-term IVIG(intravenous immunoglobulin), pulse dexamethasone or methylprednisolone, anti-D, immunosuppression with azathioprine or cyclophosphamide, vinca alkaloids, danazol, and α-interferon.(12,15)

Patients and methods:

This prospective study was conducted at Baghdad teaching hospital and included 50 patients with ITP, from November 2004 to November 2006. All patients presented with bleeding and documented thrombocytopenia by complete blood count, bone marrow examination done for all patients and showed normal or increased megakaryocytes, antinuclear factor is examined in all of patients; platelet count was done by chamber method.

Patients were excluded from the study if they had: -

1 -More than 4 criteria required for diagnosis of systemic lupus erythematosis.

2-Recent drugs ingestion that is associated with thrombocytopenia.

3-Evidencc of sepsis.

4-Evidcnce of disseminated intravascular coagulation, hemolytic uremic syndrome or thromhotic thrombocytopenia purpura.

5-Known diagnosis associated with ITP like chronic lymphatic Leukemia or lymphoma.

Steroid therapy was started for all patients as prednisone tablets 1 mg/kg/day for 4 weeks and then gradually reduced and withdrawn, patients followed with initially twice-weekly platelets count, then once weekly, patients who did not respond to or relapsed following withdrawal of steroid were offered splenectomy. Other treatment options included danazol, vincristine, intravenous immunoglobulin or intravenous dexamethasone.

Patients classified into: -

1-Satisfactory response: Platelets count more than 100 000/L

2-Partial response: Platelets count between 50000-100000/L with or without bleeding.

3-Minor or no response: Platelets count less than 50 000/L usually with bleeding.

Statistical analysis

Patients' data were tabulated and processed using SPSS 15 (Statistical package for social sciences) for windows. Qualitative data are expressed as frequency and percentage, quantitative data as mean and median. The response to therapy was calculated by Chi square test. P value less than 0.05 was considered statistically significant.

Results:

Of 50 patients, (38) were females and (12) were males, with female to male ratio (3.1:1). Median age of patients was (27), mean age (23_+10), range (17-65) years. Platelets count ranged from 2 to 88 $x10^9$/L, with mean platelet count of $32x10^9$/L at presentation as shown in table 1. Clinical manifestation of ITP included easy bruising and purpura (96 %), epistaxis (22%), gum bleeding (18%), menorrhagia (14%) and haematuria (2%).

Table1: Characteristics of 50 patients with ITP

Characteristic		Number	Percent	
Age(years)	<40	36	72	Range (17-65)
	>40	14	28	
Sex	Female	38	76	(female: male) (3.1:1)
	Male	12	24	
Platelet count	Range (2-88)$x10^9$/l	Mean 32 $x10^9$/l		

Steroid therapy was given to all patients, (20) patients not respond to this treatment (40%), (20) patients showed temporary remission (40%)and relapsed after withdrawal of steroid, (10) patients showed remission to steroid that persist even after stopping the drug, so overall response to steroid therapy is 60% as shown in table 2.

Table2: response to steroid therapy in 50 patients with ITP.

Total	Non responder	Temporary remission	Sustained remission
No. (%)	No. %	No. %	No. %
50 (100)	20 (40)	20 (40)	10 (20)

Of 20 patients (40%) who were non responders to steroid or 20 patients (40%) who relapsed after

steroid withdrawal, 6 patients achieved satisfactory response with addition of danazol 200-600mg/day with small dose of prednisone 10-15 mg /day; the rest i.e. 34 patients were advised for splenectomy, 20 patients agreed and underwent the operation; the remaining 14 patients refused and kept on steroid with or without danazol, including one pregnant patient was given intravenous immunoglobulin before labour with temporary response. All twenty patients who underwent splenectomy responded initially and did not require further treatment after withdrawal of prednisone postoperatively at (3-6) months follow up, two patients required further treatment with steroid 15-20mg/day to keep platelets count at a save level without bleeding, one patient relapsed after splenectomy and required weekly vincristine for 3 doses; as shown in table (3). Factors affecting response to steroids therapy are shown in table 4 with no significant association between responders and non responders. Table 5 shows the characteristics of patients who did splenectomy

Table (3): Overall response to splenectomy.

Total	Initial response	Sustained Response
Number %	Number %	Number %
20 100	20 100	17 85

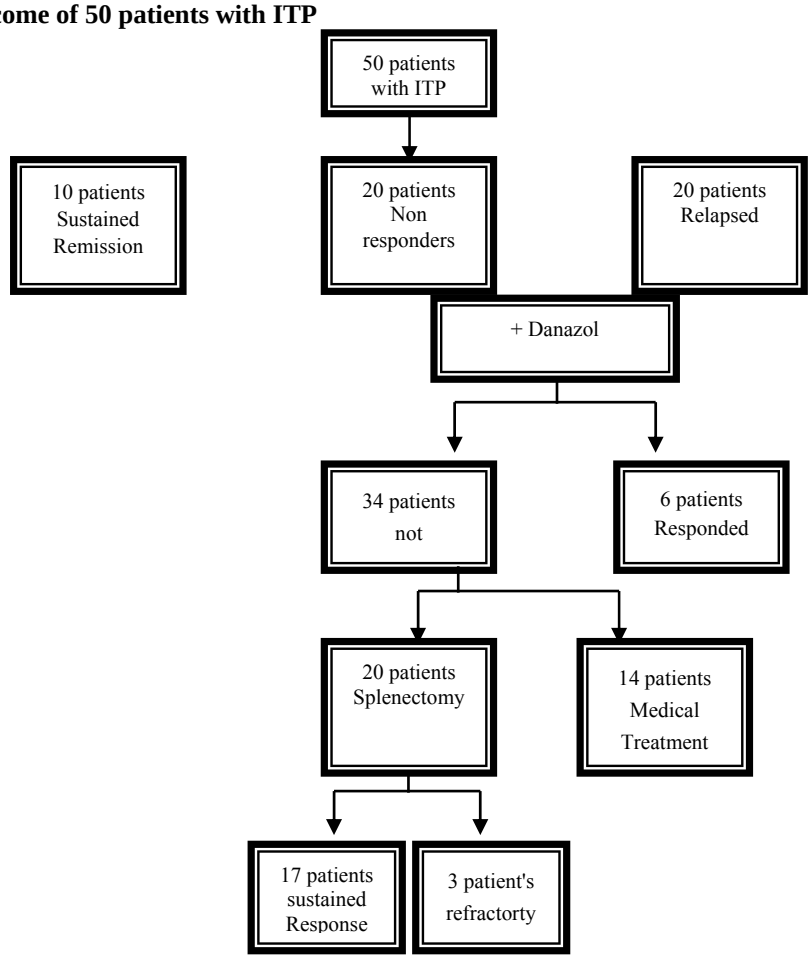
Table (4): Factors influencing the response to steroid therapy

Characteristic	Response (no.35)	No response (no.15)	P value
Age >40 <40	 8 27	 6 9	0.304
Sex Female Male	 29 6	 9 6	0.146
Platelet count >30 <30	 23 12	 8 7	0.528
Duration of bleeding >3wk < 3wk	 21 14	 9 6	0.624

Table 5 characteristic of patients underwent splenectomy

Total		Number	Percent
Age	<40	14	70
	>40	6	30
Sex	Female	15	75
	Male	5	25
Duration till surgery	>1year	15	75
	<1year	5	25
Steroid response	No response	12	60
	Relapsed	8	40

Diagram: outcome of 50 patients with ITP



Discussion:

The present prospective study describes the clinical outcomes of 50 adult ITP patients. Regarding sex distribution is there was female predominance with female to male ratio of (3.2:1); this is similar to previous studies (3, 4, 8, and 18). The age distribution is as follow: range (17-65 years), with median of 27 years, this is similar to previous study by Stasi et al who found that about 74% of 934 cases were younger than age 40 (range, 16 to 87 years of age)(18), but different from other studies (3,8) . No significant differences were seen between low- and high-dose steroid regimens in several studies. Mazzucconi and colleagues randomized patients between 0.5 mg/kg/day and 1.5 mg/kg/day. The response rates in adults were not significantly different between patients treated with low- versus high-dose steroids, 30% and 34% complete response, respectively (17). However, based on the opinion of an expert panel convened by the American Society of Hematology, high-dose prednisone (1 to 2 mg/kg/day) is recommended as appropriate initial treatment in ITP patients with platelets <30,000/µl, including asymptomatic Patients (12). In this study all patients were given Steroid therapy as (1 mg/kg/day), sixty percent showed initial response, this is different from Iraqi study done by Alkhalisi et al where he found that response to steroid was occurred in (75 %)(16) ,while Mazzucconi and Stasi et al documented response to steroid of (38.8%) and (34%) respectively (17,18). Sustained responses after discontinuation of the drug occur in only 20% of patients in this study, this is higher than (12.5%) by Alkhalisi (16), but lower than (25%) by George et al (2). Age, sex and platelets count had no significant effect on achieving response to steroid therapy as shown by this study; our result was similar to that reported in the literature(8) , but Shamebo et al found that duration of bleeding significantly affect the response, if patient presented with duration of bleeding less than 3 weeks, so those patients significantly respond better to steroid(20); in our study no such relationship was found because most of patients presented with duration of bleeding of more than 3 weeks. As shown in this study and by other investigators (2, 4, 9, 13, 18), splenectomy is the most successful therapeutic approach in ITP because it produced the highest rate of Initial response (100% of all 20 patients); this is higher than (94.6%) by Iraqi study (16), (50%), by Ethiopian study respectively (20), this is may be due to smaller number of patients and shorter period of follow up. On the other hand a recent population-based study suggests that adult ITP is a more benign disease than previously suspected, with frequent remissions that occur spontaneously or in response to first-line therapy and with a low requirement for splenectomy. (19). The beneficial effect of splenectomy, unlike that of corticosteroids are unaffected by the interval between the onset of disease and treatment. Nevertheless, because major surgery is involved, it has usually been considered as treatment of second choice following a demonstrated lack of response to steroid .from the present experience ,however, this viewpoint seems valid only to patient with acute ITP and less so for patients with chronic ITP where response to corticosteroid is poor and always much worse than that obtained with splenectomy.therefore it seem rational to propose splenectomy as initial or early treatment of choice for patients with chronic ITP because use of corticosteroids ,especially for prolong period ,result in increases risks and unwanted side effects.(4)

Conclusion:-

This study suggests that splenectomy remains the most effective treatment for patients who were non responder to or relapsed after steroid therapy.

The majority of patients who underwent splenectomy obtained complete remission, while only minority of those who did not have this therapeutic modality were likely to sustain similar results

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