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A RETROSPECTIVE ANALYSIS OF THERAPEUTIC OUTCOMES, LABORATORY & CLINICAL FEATURES OF THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

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Abstract:

Objective: *We aimed to evaluate an overall response rate in the patients of TTP (Thrombotic Thrombocytopenic Purpura), as it is considered among the diseases which pose a serious threat to life.*

Methods: *Our retrospective research was carried out on twenty-four patients treated at Sir Ganga Ram Hospital, Lahore from May 2016 to April 2017. We included TTP cases having MAHA (Microangiopathic Hemolysis) and thrombocytopenia. Clinical and laboratory features were assessed in this research in the twenty-four hours treatment cycle.*

Results: *We included six males and eighteen female patients with a female dominant sample size. The factor of mean age was observed as (33.5 ± 13.9) years. Neurologic abnormalities included 7 cases of fever (29%), 22 neurologic features (91%), 10 renal impairment (42%), 4 cardiac manifestations (20.83%), 22 triad (91.7%) and 2 TTP pentads (8.2%). Majority cases were of idiopathic TTP (54.16%). Every case received TPE (Therapeutic Plasma Exchange); 23 were given adjunctive corticosteroids (95.8%) and 13 rituximab (54.2%) because of TPE refractoriness earlier or at the seventh day. Complete remission was completed by 24 cases (87.5%) with no relapse signs. Disease severity and late reporting caused three deaths and 20 cases survived (83.3%).*

Conclusion: *TPE, rituximab or steroids are very much effective for the prevention of mortality and in order to achieve complete remission in the patients. Early referral and diagnostic awareness are mandatory for a timely extension of healthcare facilities to the TTP affected patients.*

Keywords: *Therapeutic Plasma Exchange (TPE), Rituximab, Microangiopathic Hemolysis (MAHA) and Thrombotic Thrombocytopenic Purpura (TTP).*

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INTRODUCTION:

TTP is characterized by the disposition of microvascular platelet and formation of thrombus which causes MAHA; fever, neurologic deficits and renal failure also accompany thrombocytopenia. Von-Willebrand (vW) factor deficiency cleavage metalloprotease is also taken as (ADAMTS – 13) which is an important implicating TTP factor. The existence of congenital TTP in a number of TTP sporadic cases is linked to (ADAMTS – 13) deficiency because of autoantibodies resistance [1]. A huge amount of vW is stored as a result of endothelial damage as ULMM (Ultra-Large Multimers) in bodies of Weibel Palade which is released through circulation.

As a result of (ADAMTS – 13) deficiency, splicing of ULMM cannot be made. Platelets are attracted by ULMM for the formation of platelet thrombi. Platelets consumption in platelet-rich thrombi causes thrombocytopenia (Platelets normally 10 – 30 x 10 ^ 9 / l). These thrombi cause cerebral and renal damage and also damage related organ systems [2 – 5]. Stroke, myocardial infarction, transient ischemic attacks, arrhythmia, azotemia and bleeding are included in acute morbidities. Precipitate fetal loss during pregnancy is also caused by TTP [1]. TTP diagnosed cases should be initiated treatment on the basis of thrombocytopenia and MAHA in the meantime of four to eight hours even if there is no sign of renal impairment, CND or fever [6]. Ninety percent of cases of TTP are fatal before the introduction of TPE and survival rate was revived by 90% through timely diagnosis [7, 8]. Major treatments are immunosuppressive and TPE therapies. Few reports also available in the published literature of the Middle East as well [9 – 11]. We aimed to evaluate an overall response rate in the patients of TTP (Thrombotic Thrombocytopenic Purpura), as it is considered among the diseases which pose a serious threat to life.

METHODS:

Our retrospective research was carried out on twenty-four patients treated at Sir Ganga Ram Hospital, Lahore from May 2016 to April 2017. We included TTP cases having MAHA (Microangiopathic Hemolysis) and thrombocytopenia. Clinical and laboratory features were assessed in this research in the twenty-four hours treatment cycle. Our criteria for the disease diagnostic included thrombocytopenia without any diagnosed cause as (< 100 ^ 109 / L), high LDH and MAHA having schistocytes as observed through peripheral blood smear. We did not include related thrombotic microangiopathies such as cancer, DIC and preeclampsia.

Regular clinical assessment of blood cell counts, coagulation profile, reticulocyte count, serum lactate dehydrogenase (LDH), serum creatinine, bilirubin and cardiac enzymes was carried out. Possible levels of (ADAMTS – 13) and titer inhibition was also determined.

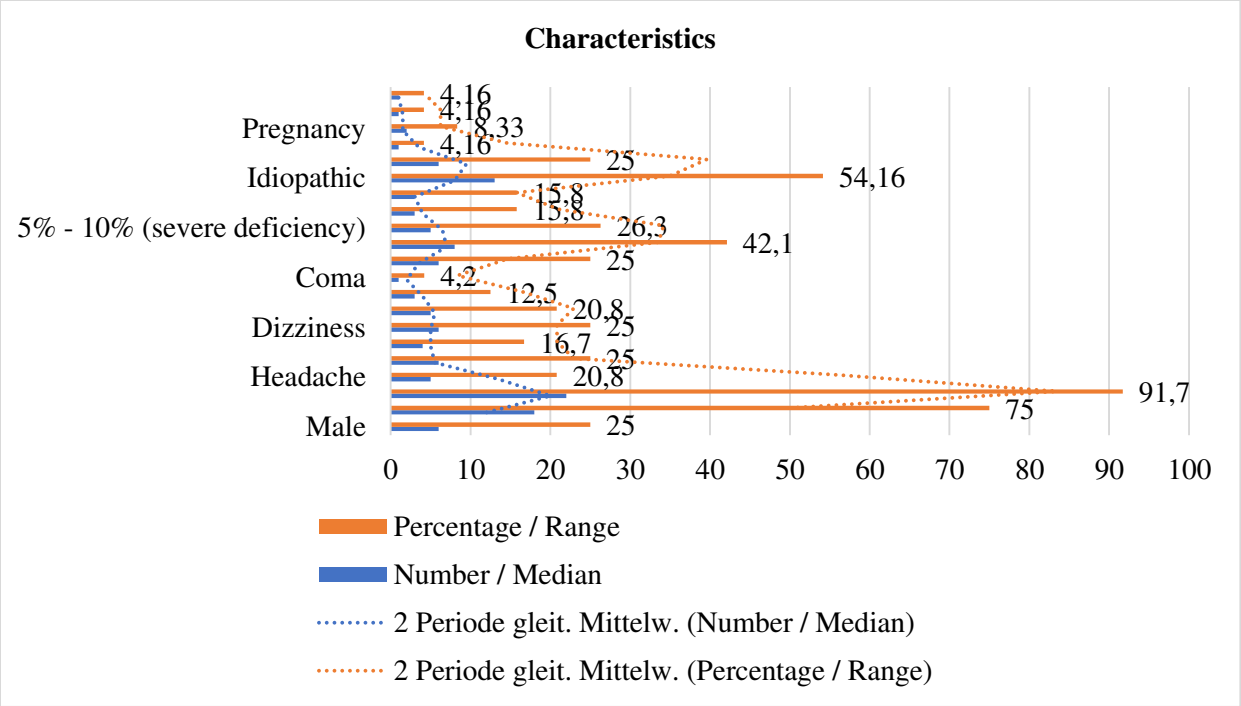
Continues variables were reflected in (Mean ± SD), median & ranges. SPSS and paired sample T-test was applied ($P < 0.05$).

RESULTS:

Detailed outcomes analysis of platelet counts paired comparison, LDH, Hemoglobin on the first and seventh day, outcomes, therapeutic details and complications and patient's characteristics have been shown in the tabular data. Outcomes are presented in number, median, percentage and range form.

Table – I: Characteristics of the 24 TTP patients.

Characteristics		**Number / Median**	**Percentage / Range**
Age (Range), median		33.5	17 - 63
Gender	Male	6	25
	Female	18	75
Neurological	Neurological manifestations	22	91.7
	Headache	5	20.8
	Confusion	6	25
	Psychiatric symptoms	4	16.7
	Dizziness	6	25
	Seizures	5	20.8
	TIA	3	12.5
	Coma	1	4.2
	Stroke	6	25
Fever		7	29.1
Renal manifestations		10	41.7
Patients with triad (MAHA + Neurological + thrombocytopnia)		22	91.6
Patients with TTP pentad		2	8.3
Cardiac manifestations		4	16.6
Symptomatic Thrombocytopenia		11	45.8
Hemoglobin g/dl Median (Range)		8.25	4.08 - 13.6
Platelets x10^9/l Median (Range)		14	5 - 57.9
LDH IU/L Median (Range)		981	186 - 4413
Bilirubin Total umol/l Median (Range)		30.4	3.6 - 127
Bilirubin Indirect umol/l Median (Range)		24.3	2.6 - 87
Creatinine umol/l Median (Range)		84	44 - 699
ADAMTS13 activity %	< 5% (very severe deficiency)	8	42.1
	5% - 10% (severe deficiency)	5	26.3
	10% - 50% (Low)	3	15.8
	> 50% (Normal)	3	15.8
Plausible Etiological Factors	Idiopathic	13	54.16
	SLE	6	25
	Pregnancy + SLE	1	4.16
	Pregnancy	2	8.33
	Malignancy (multiple myeloma)	1	4.16
	Congenital + Pregnancy	1	4.16
Follow-up time months' median (range)		22	1 - 113



We included six males and eighteen female patients with a female dominant sample size. The factor of mean age was observed as (33.5 ± 13.9) years. Neurologic abnormalities included 7 cases of fever (29%), 22 neurologic features (91%), 10 renal impairment (42%), 4 cardiac manifestations (20.83%), 22 triad (91.7%) and 2 TTP pentads (8.2%). Majority cases were of idiopathic TTP (54.16%). Every case received TPE (Therapeutic Plasma Exchange); 23 were given adjunctive corticosteroids (95.8%) and 13 rituximab (54.2%) because of TPE refractoriness earlier or at the seventh day. Complete remission was completed by 24 cases (87.5%) with no relapse signs. Disease severity and late reporting caused three deaths and 20 cases survived (83.3%).

Table – II: Paired comparison analysis of Platelet count, Hemoglobin and LDH on Day1 and Day7 of TPE

Parameters	Minimum	Maximum	Mean	±S.D	P-values
Plt count Day - 1 of TPE	5	57.9	18.77	14.13	< 0.001
Plt count Day - 7 of TPE	22	419	155.92	112.8	
Hgb D1 of TPE	4.08	13.6	8.21	2.01	0.007
Hgb D7 of TPE	7.26	12.9	9.52	1.38	
LDH D1 of TPE	186	4413	1211.2	971.4	< 0.001
LDH D7 of TPE	131	463	278.92	87.93	

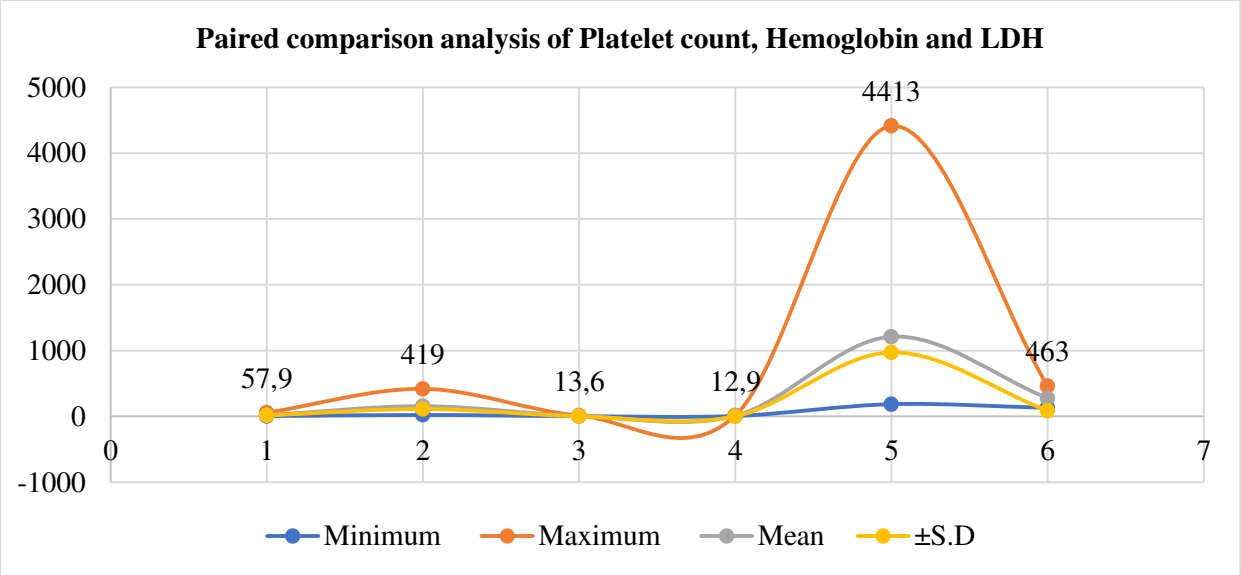
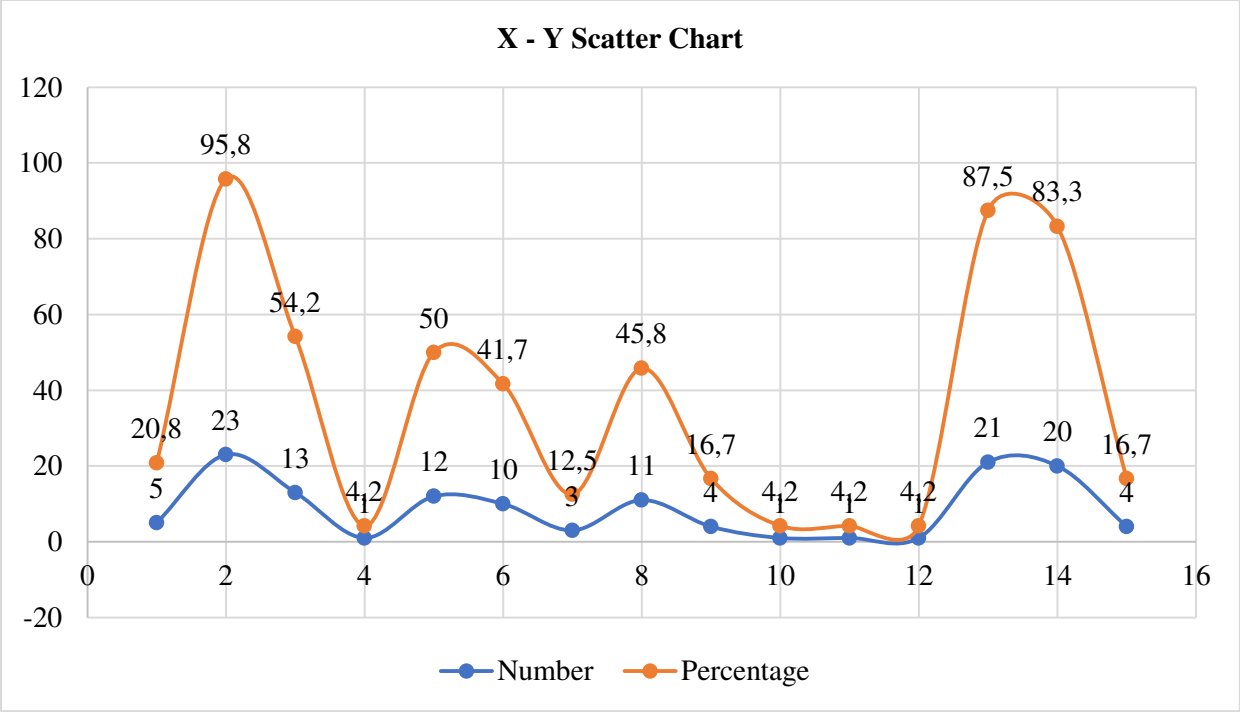


Table – III: Therapy details, complications and outcome of 24 patients with TTP.

Therapy details, complications and outcome		Median / Number	Range / Percentage
Number of TPE		15.5	1–52
Inpatient days		27	1–131
Follow up time		22	1–113
Average plasma volumes		1.2	1–1.5
Early refractory		5	20.8
Steroids Received		23	95.8
Rituximab	Rituximab Received	13	54.2
	Rituximab 1000 mg (in SLE patient)	1	4.2
	Rituximab 375 mg/m^2	12	50
ICU needed		10	41.7
Line related complications		3	12.5
Platelet transfusion needed for line insertion		11	45.8
Infection		4	16.7
Isolated organisms	Acetinobactor	1	4.2
	Klebsiella	1	4.2
	Pseudomonas	1	4.2
	Remission Achieved	21	87.5
	Alive	20	83.3
	Dead	4	16.7



DISCUSSION:

A large number of TTP cases have been studied in various studies but they lack clinical features and therapeutic outcomes [9 – 13]. In this case, neurologic features were observed in (91.7%) cases. Whereas, a classic pentad such as anaemia, fever, thrombocytopenia, renal and neurologic abnormalities were found in only (8.3%) cases. Which can be compared with the outcomes of Radolfi et al. [14].

Male and female groups have variation in the significant literary evidence [15, 16]. Women were dominating men in our research with a proportion of three to one and median age as (33.5 years) in the range of (17 – 63) years. Age and sex distribution are the same as observed in various other international research studies [12, 13]. TTP can be may be acquired or congenital.

There were few acquired factors such as SLE-related and pregnancy-related having a respective proportion of 29.2% & 16.66. One case was classified as congenital TTP and 13 cases as idiopathic. Our TTP predisposed factor had a minute variation with the other authors [17, 18].

ADAMTS-13 regulates the adhesion of platelet adhesion and accumulates through vWF multimers cleavage, this ADAMTS-13 level activity is controversial in TTP [18, 19]. According to Coppo 71% cases were diagnosed with TTP clinically and severe deficiency of ADAMTS-13 was also reported in these cases [20].

Nineteen cases were observed with an activity of ADAMTS-13; we also found a severe deficiency of ADAMTS-13 in 8 cases (42.1%), 4 idiopathic cases, 5 severe deficiency cases (26.3%), 3 reduced activity (15.8%); whereas, 3 cases were normal (15.8%). Contrarily, Vesely considered severe ADAMTS-13 deficiency as a vital idiopathic TTP marker [5].

However, it was learned through our outcomes that in the normal range of ADAMTS-13 activity TTP diagnosis is difficult. Clinical conditions such as SLE, DIC, ITP and liver cirrhosis also reported slight decreased in the activity of ADAMTS-13 [15, 21 – 23]. About 44% – 93% of TTP cases reported inhibitory antibodies against the activity of ADAMTS-13 as in nine patients six patients (66.6%) were observed (0.425 BU) titer range. TPE was given to every patient. On the first and seventh day of TPE, Median platelet count ($P < 0.001$), haemoglobin ($P < 0.007$) and LDH ($P < 0.001$) were significant which reflects the effectiveness of therapy. Our findings of the early TPE refractory, rituximab, neurological or cardiac involvement are comparable with the outcomes of Scully [19]. Complete remission rate was (87.5%) with a survival rate of (83.3%) as three deaths were also reported. No relapse was reported which is in contrast with the various other research studies about relapse rate (30% – 50%) [5, 24]. No

serious rituximab complications were observed in prolonged follow-up and no leukoencephalopathy case.

Adverse events are associated with TPE [25]. TPE related complication was reported in 3 cases (12.5%) having one case of accidental removal, haemorrhage and line blockage. Platelet transfusion was required in 11 cases (45.8%) before insertion of line and 4 cases (16.7%) developed an infection with Klebsiella pneumoniae, Acinetobacter or Pseudomonas. Ten cases were critical to the admission (41.7%), they were treated with the support of ICU as clinical reports suggested which is comparable with the outcomes of Scully [19].

CONCLUSION:

No doubt, TTP is a disease which poses a threat to life and it needs a rapid treatment. TPE, rituximab or steroids are very much effective for the prevention of mortality and in order to achieve complete remission in the patients. Early referral and diagnostic awareness are mandatory for a timely extension of healthcare facilities to the TTP affected patients.

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