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RESEARCH ARTICLE

Thrombotic thrombocytopenic purpura: Combined plasma exchange, fresh frozen plasma and corticosteroids

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Abstract

Background: Plasma exchange (PEX) plays an important role in the management of thrombotic thrombocytopenic purpura (TTP). Some studies had recommended the use of fresh frozen plasma (FFP) alone or with PEX. The use of corticosteroids was tried only in some studies with variable responses. This work was a retrospective study, carried out in the Plasma Exchange Unit, Zagazig University, Egypt, to study the outcome of the applied protocol of management of TTP, using combined therapeutic PEX, FFP infusion and pulse corticosteroids.

Subjects and Methods: This study included 38 patients (28 females and 10 males) with TTP, mean age (37.1±12.7) years, referred to the Plasma Exchange Unit in the period from (2009-2013). They were divided into 2 groups as regards the therapy they received: Group I: 26 TTP patients (18 females and 8 males), who received daily plasma exchange sessions for 5 days, followed by every other day sessions, FFP infusion during and in-between sessions, in addition to methyl prednisolone pulse therapy followed by oral predinsolone, and Group II: 12 TTP patients (10 females and 2 males), who escaped one or more of the therapeutic protocol.

Results: The overall survival among all the 38 TTP patients included 27 patients (71.1%); {19 females (67.9%) and 8 males (80%)}, in group I (26 patients), it included 24 patients (92.3%), {17 females (94.4%) and 7 males (87.5%)}, while in group II (12 patients), it included 3 patients (25%), {2 females (20%) and one male(50%)}. The overall number of plasma exchange sessions ranged from (1-14 sessions), with a mean of (7.1±3.5 sessions). Patients who died had sepsis, incomplete plasma removal, missed sessions, inadequate FFP infusion, delayed referral for plasma exchange, lack or delay of steroid use, complications related to TTP or plasma exchange itself or alternate diagnosis.

Conclusion: The combined therapy for TTP, using a strict protocol of daily total volume PEX for 5 successive days, followed by every other day sessions, FFP infusion during and in-between sessions, in addition to methyl prednisolone pulse therapy, followed by oral prednisolone improves the outcome in TTP patients.

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder, with a reported incidence of six cases per million per year in the UK. It is an important diagnosis to make because the untreated mortality is 90%, which can be reduced with prompt therapy with plasma exchange (PEX) (1). The classic pentad of diagnostic features (Micro-

angiopathic hemolytic anemia (MAHA) (schistocytes), thrombocytopenia, fluctuating central nervous manifestations, renal impairment and fever) has been recognized for many years. However, several other syndromes are also characterized by similar features. These include haemolytic uraemic syndrome (HUS), eclampsia , disseminated intravascular coagulopathy (DIC) and the HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) (2). TTP can present without the full pentad; up to 35% of patients do not have neurological signs at presentation and renal abnormalities and fever are not prominent features. The revised diagnostic criteria state that TTP must be considered in the presence of thrombocytopenia and MAHA alone (3). Patients are described as having idiopathic TTP if they have no apparent other condition that may cause thrombotic microangiopathy and they commonly have severe ADAMTS13 deficiency and a higher survival rate. Patients are described as having secondary TTP if other conditions are identified that may cause thrombotic microangiopathy, such as hematopoietic stem cell transplantation (HSCT), pregnancy, drug association, other autoimmune diseases, HIV infection, and cancer , while they rarely have severe ADAMTS13 deficiency and poor survival (4). Congenital and acute acquired TTP are due to a deficiency of von Willebrand factor (VWF) cleaving protein, also known as ADAMTS13, where ultra large multimers of VWF (ULVWF) released from endothelium are not cleaved appropriately, and cause spontaneous platelet aggregates in conditions of high shear, such as in the microvasculature of the brain, heart and kidneys (5). Patients with congenital TTP have persistently low levels of ADAMTS13, but they can be asymptomatic until a further precipitating event results in a frank TTP episode. Events include febrile episodes, infections, vaccinations, excess alcohol intake and pregnancy (6). Presenting symptoms and signs of TTP may be related to thrombocytopenia (epistaxis, bruising, hematuria, menorrhagia), CNS manifestations in 70-80% (headache, confusions, paresis, fits, encephalopathy, coma), fever, microangiopathic hemolysis (pallor, jaundice), organ ischemia (chest pain, abdominal pain), renal affection (proteinuria, hematuria), but acute renal failure is very rare (7). Consumption of platelets in platelet-rich thrombi results in thrombocytopenia. The median platelet count is typically 10.000-30.000 / dl. Mechanical fragmentation of erythrocytes during their flow through partially occluded, high shear small vessels causes a MAHA. Median haemoglobin levels on admission are typically 8.0–10.0 g/dl, with schistocytes in the film, low haptoglobin levels and raised reticulocyte counts due to haemolysis. The direct Coombs test is negative. The combination of haemolysis and tissue ischaemia produces elevated lactate dehydrogenase (LDH) values. The clotting screen (prothrombin time, activated partial thromboplastin time and fibrinogen) is usually normal (8). Thrombocytopenia is usually more severe in cases without predominant renal involvement; the platelet count are usually as low as < 20,000/mm3 at presentation. Proteinuria, microscopic hematuria, granular or red cell casts may be seen with renal involvement (9). Although the mean platelet count is lower in TTP than HUS (18.000/dl vs. 36.000/dl), there is a wide range and considerable overlap. Severe thrombocytopenia at diagnosis (platelet count < 20.000 /dl) has been suggested to be a poor prognostic indicator, conferring increased mortality, although this is not a uniform observation. Examination of the blood film usually shows striking red cell fragmentation and polychromasia, but schistocytes may be absent from the peripheral blood film in the first 24–48 h following clinical presentation (10). At presentation, the clinical distinction between idiopathic TTP, various forms of secondary thrombotic microangiopathy, and even Shiga toxin-associated hemolytic uremic syndrome (HUS) can be problematic because the symptoms and laboratory findings often overlap. Consequently, plasma exchange usually is administered to any patient with thrombotic microangiopathy if there is doubt about the cause. Plasma exchange can induce remissions in approximately 80% of patients with idiopathic TTP, but patients have a much worse prognosis when thrombotic microangiopathy is associated with cancer, certain drugs, infections, or tissue transplantation (11). Plasma exchange should be instituted within 24 hours of presentation as delay in treatment initiation may increase treatment failure and it would seem appropriate to commence plasma exchange as soon as practicable if renal impairment, cardiac failure or coma is present. The average number of procedures required for remission is usually 15·8 (range 3–36) sessions. As the premature omission of a single plasma exchange may be associated with exacerbation, patients should be treated in centers able to provide daily sessions (12). One hundred two patients with thrombotic thrombocytopenic purpura have been randomly assigned to receive either plasma exchange or plasma infusion with fresh-frozen plasma on seven of the first nine days after entry into the trial. Plasma exchange has been found to be more effective than plasma infusion in the treatment of thrombotic thrombocytopenic purpura (13). The frequency of PEX-related major complications has decreased from 1996 to 2011, possibly due to the increased use of corticosteroids and rituximab and the decreased duration of PEX required to achieving remission (14). Remission is defined as the maintenance of a normal platelet count (≥ 150.000/dl) and the absence of hemolytic anemia without immunosuppressive medication or plasma exchange, while relapse is defined as an episode of acute TTP more than 30 days after remission, and occurs in 20–50% of cases (15). Splenectomy remains an option for patients with refractory or relapsing TTP, with minimal morbidity and mortality and achieves a greater than 80% response rate. The laparoscopic approach is favored because it is associated with fewer complications

Subjects and Methods

This study has been carried out at the Plasma Exchange Unit, Internal Medicine Department, Zagazig University, Egypt. It was a retrospective study analyzing the data of 38 TTP patients (28 females and 10 males), referred for plasma exchange from (2009-2013), of which 26 TTP patients (Group I) (18 females and 8 males) strictly followed the applied protocol, while 12 TTP patients (Group II) (10 females and 2 males) missed one or more parts of that protocol. They had been diagnosed as cases of thrombotic thrombocytopenic purpura (TTP) (Microangiopathic hemolytic anemia (MAHA), fragmented RBCs on peripheral blood film, schistocytes, thrombocytopenia, elevated LDH, reticulocyosis, increased total and indirect bilirubin, negative direct Coomb's test, normal PTT, PT, INR), with/without CNS manifestations (fits, confusion, coma), renal manifestations and fever). Other similar conditions were excluded (hemolytic uremic syndrome (HUS), eclampsia, HELLP syndrome and DIC). All patients have been screened for HIV, hepatitis B and hepatitis C and common autoantibodies, including antinuclear antibodies (ANA), while some patients had bone marrow examination after their platelet count reached 60.000/cc. Other investigations for the complications of TTP have been done for patients according to their condition; CT brain, ECG, chext X-ray, abdominal ultrasound, blood electrolytes, arterial blood gases, serum Troponin, D-Dimer, blood urea, serum creatinine, liver function tests, complete blood picture, ESR, blood culture, urine culture and other tests, as required. We analyzed their data, as regards their age, sex, general condition at referral, time interval before referral for plasma exchange unit, associated symptoms and signs of TTP, possible etiology, laboratory investigations before, during and after starting plasma exchange, weight, site of venous access, plasma volume removed, plasma volume replaced, replacement fluids, complications of plasma exchange, FFP infusion during and in-between sessions, number of sessions, time schedule of sessions, dose of anticoagulants, use of corticosteroids, use of immunosuppressive drugs, use of other medications, outcome, relapse, possible cause of death (in the cases which died) , so that we may have some useful recommendations about the best applied protocol for better outcome. ADAMTS13 was not measured, the possible underlying cause was not diagnosed in most patients and patients with TTP who were not referred to Plasma Exchange Unit were not included. The combined therapy (daily total plasma exchange for 5 successive days, followed by every other day sessions, fresh frozen plasma during and in-between sessions and pulse methyl prednisolone, followed by oral steroid) had been applied during the period (2009-2013). Methyl prednisolone was started immediately after TPP diagnosis and had been given after plasma exchange sessions (to avoid its removal) as a pulse therapy 0.5-1.0 gm/day/3-5 days, followed by oral prednisolone 1-2 mg /kg /day , continued for up to 2 weeks after complete remission and then gradually tapered. Even before starting plasma exchange sessions, most patients immediately received FFP (2 units/ 8 hours), till plasma exchange had been arranged. Then the plasma infusion had been continued after starting plasma sessions; using FFP (2 units / 8 hours), which had been continued for a few days after platelet correction to ensure remission. Plasma exchange sessions had been started as early as possible, once daily, for the first 5 sessions, then every other day, according to response and severity, till platelets had increased to 150.000/cc and schistocytes had disappeared, and then sessions had been continued for 1-2 more sessions to make sure of response. According to hemodynamic state of the patient, we had started with plasma exchange 1-1.5 plasma volumes removal (40-80 ml/kg, up to 4 L), corrected for weight and hematocrit value, and then maintained at 1.5 plasma volumes removal in subsequent sessions, to avoid hypotension and vomiting that occurs during the first sessions. The number and schedule of sessions had been tailored according to every individual case. Volume replacement had been done using saline 0.9% during the sessions, in addition to fresh frozen plasma (FFP) at the last part of sessions (6-8 units). Unfractionated low molecular weight heparin (LMWH) had been used in a higher dose than recommended, 20.000-25.000 units/session, according to age and weight, because it had been given in saline infusion (recommended dose of 100 units/ kg), as lower doses had been associated with blood clotting in the filters. Most patients had received broad spectrum antibiotics and some received antiepileptic treatment for seizures. Plasma exchange sessions had not been stopped immediately when platelet count reached 150.000/dl, but we had continued sessions at lower frequency, till we had confirmed remission and excluded relapse. Other markers of remission had included reticulocytic count, LDH, total and indirect bilirubin, Hb%, absence of fragmented RBCs or schistocytes in peripheral blood film and clinical improvement of CNS, bleeding or thrombotic manifestations. The color of removed plasma had been additionally used an indicator of continuing hemolysis (clear, yellow fluid indicated good response and reduction of hemolysis). Most patients with platelet count less than 60.000/dl had a femoral catheter inserted for plasma exchange and its site had been changed every 3-5 days to avoid thrombosis or infection. Patients with platelet count more than 60.000/dl had a jugular venous catheter carefully inserted with a following chest X-ray to exclude pneumothorax/hemothorax. Patients with hemoglobin ≤ 7 gm/ dl had received packed RBCs, while none of our patients received platelets transfusion after referral (contraindicated), although some of them had already received platelets transfusion before admission to hospital or before TTP had been diagnosed. Most of the patients required ICU admission and a few of them had required artificial ventilation. One female patient with relapse, in spite of adequate plasma exchange and immunosuppressive therapy,

required splenectomy, with good response. Patients with proved alternate diagnosis were excluded from this study (except those who died, while being treated as TTP, but might have had possible alternative diagnosis).

Results

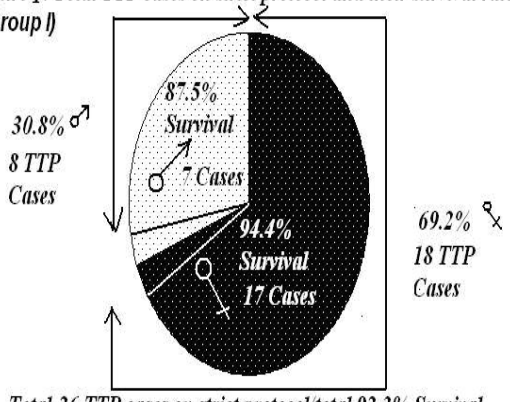
Over the period from 2009 till 2013, 38 cases of TTP were referred for plasma exchange; 28 females (73.6%) and 10 males (26.4%), mean age (37.1±12.7) years, of which only 27 patients (71.1%) survived (19 females and 8 males). Among the 26 TTP patients (Group I) {18 females (69.2%) and 8 males (30.8%)}, who strictly adhered to the protocol and received the combined therapeutic plasma exchange, FFP infusion, and corticosteroids, 24 patients (92.3%) survived {17 of 18 females (94.4%) and 7 of 8 males (87.5%)}, while among the 12 TTP patients (Group II) {10 females (83.3%) and 2 males (16.7%)}, in which one or more parts of that protocol were missing, 3 patients (25%) survived (2 of 10 females) (20%) and (1 of 2 males) (50%)). Survival in TTP patients according to their age was as follows: (less than 20 years) 3 of 4 cases (75%), (21-30 years) 6 of 8 cases (75%), (31-40 years) 8 of 12 cases (66.6%), (41-50 years) 5 of 7 cases (71.4%), (51-60 years) 3 of 4 cases (75%) while more than 60 years 2 of 3 cases (66.6%). Patients who had CNS manifestations included 30 cases (78.9%), of which 23 cases (76.6%) survived, while 8 cases (21.1%) did not have CNS manifestations, of which 4 cases (50%) survived. Patients who had renal manifestations in the form of mild renal impairment or proteinuria included 7 cases (18.4%), of which 5 cases (71.4%) survived, while 31 cases (81.6%) did not have renal manifestations, of which 22 cases (70.9%) survived. Patients who had infection, fever or leucocytosis included 26 cases (68.4%), of which 16 cases (61.5%) survived, while 12 cases (31.6%) did not have infection, fever, or leucocytosis, of which 11 cases (91.6%) survived. Patients with septicemia and/or septic shock included 9 cases (23.6%), none of them survived. Patients in whom basic platelet count was less than 20.000/dl included 20 cases (52.6%), with survival in 13 cases (65%), while 18 cases (47.4%) had basic platelets count 20.000/dl or more, with survival in 14 cases (77.7%). Patients with basic Hb% less than 7.0 gm/dl included 19 cases (50%), with survival in 13 cases (68.4%), while 19 cases (50%) had basic Hb% 7.0 gm/dl or more, with survival in 14 cases (73.6%). The number of plasma exchange sessions ranged from (1-14 sessions), with a mean of (7.1±3.5) sessions. Patients who had less than 5 sessions included 10 cases (26.3%), none of them survived, while patients who received 5 or more sessions included 28 cases (73.7%), of which 27 cases (96.4%) survived. Patients with one plasma volume removal included 6 cases (15.7%), none of them survived, while patients with 1.5 plasma volume removals included 32 cases (84.2%), of which 27 cases (84.3%) survived. From 2009 to 2013, more experience and strict compliance to the applied protocol resulted in gradual improvement in the outcome of TTP cases, referred to plasma exchange unit and overall survival improved from 2009 (40%) to 2013 (88.8%). Patients who died were among patients who had severe sepsis, abscesses, septicemia, leucocytosis, severe hypoalbuminemia, severe anemia at the start, severe thrombocytopenia at the start, delay in the diagnosis and referral, inadequate fresh frozen plasma during and in-between sessions due to unavailable patient's blood group, omission or delaying of one session or more, incomplete plasma volume exchange, relapse after original temporary improvement, using azathioprine before referral, inadequate steroid use, lack of hygiene , infection at the site of venous catheter, Foley's catheter or venous cannulae, thrombosis at the site of venous catheter, deep venous thrombosis, embolism, or compulsive cessation of plasma exchange due to hemodynamic instability or lack of response, while patients with proved alternate diagnosis were excluded from this study. Fresenius AS 104 Blood Cell Separator was used, with pL1 filters, for PEX.

Table 1: **TTP management protocol in Plasma Exchange Unit, Zagazig University, Egypt**

Diagnosis	**MAHA, Schistocytes, thrombocytopenia, with/withou CNS, renal manifestations or fever.**	**ADAMTS13 was not measured (not available). Exclusion of other similar conditions.**
Treatment	**Immediately start pulse methyl prednisolone 0.5-1.0 gm/day/3-5 days. (after sessions, when PEX is started)**	**Then continue with oral prednisolone 1-2 mg/kg/day for up to 2 weeks after complete remission, then gradual tapering.**
	Immediately start FFP infusion, 2 units/8 hours.	**Continue after plasma exchange, 2 units/8 hours (infusion given after sessions, not before).**
	Immediately start plasma exchange, as early as possible. Remove 1.0-1.5 plasma volumes/session (40-80 ml/kg, up to 4 L). Replace with FFP, 6-8 units at the last part of sessions.	**Adjust plasma exchange volume according to weight and hematocrit. 1.5 plasma volume removal is preferred, if no hemodynamic instability. Use normal saline 0.9% for replacement during sessions**

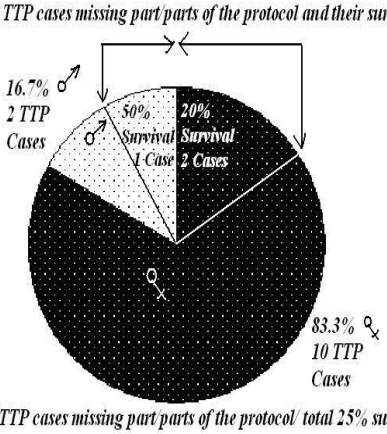
	Daily PEX sessions are given for the first 5 days, followed by every other day sessions.	**Sessions can be modified according to severity and response. No omission of sessions at first sessions to avoid rebound thrombocytopenia.**
	LMWH should be given at larger doses (20.000-25.000) units, according to age and weight, than recommended, if given in saline infusion, to avoid thrombosis.	**Sessions should not be stopped suddenly and 1-2 sessions may be offered until complete remission is proved (unless no response or other diagnosis is proved).**
Follow up	**Daily blood film, platelet count, Hb%, reticulocytic count, LDH, and color of removed plasma. Follow up should be continued for 6 months, to ensure remission and detect relapse.**	**If no response after first session, continue for 1-2 more sessions, with more intense plasma exchange. Additional investigations to detect other diseases causing secondary TTP or diagnosis of diseases other than TTP are required.**
Other measures	**Strict caution during venous catheter insertion, to avoid bleeding. Strict antiseptic conditions, to avoid catheter infection. Catheters should be immediately removed, if infected. Site of catheter should be changed every 3-5 days, to avoid thrombosis.**	**If platelet count is less than 60.000/ml, femoral catheters are preferred. If platelet count is more than 60.000/ml, jugular catheters are preferred. (Chest x-ray should be done to exclude pneumothorax/hemothorax)**
	Broad spectrum antibiotics should be immediately started and continued, even if there are no signs of infection.	**Patients should be admitted to ICU, especially in the first week, or when they have serious complications.**
	Symptomatic treatment for convulsions, thrombosis, infections, bleeding, infection, fever, and other complications, should be started, as required.	**Avoid platelet transfusion. Packed RBCs can be given if Hb% is less than 7 gm/dl. Splenectomy may be required for relapse, not responding to PEX or immunosuppression**

Figure 1: Total TTP cases on strict protocol and their survival rates (Group I)



Total 26 TTP cases on strict protocol/total 92.3% Survival

Figure 2 : Total TTP cases missing part/parts of the protocol and their survival rates (Group II)



Total 12 TTP cases missing part/parts of the protocol/ total 25% survival

***Table 2*: Showing TTP cases referred to plasma exchange unit according to their management protocol and response**				
No. of TTP cases (Females/	**Total 38 cases {28 Females**	**Group I 26 cases (68.4%)**	**Group II 12 cases (31.5%)**	**P value**

Males)	**(73.6%) 10 Males (26.4%)}**	**{18 Females (69.2%) 8 Males (30.8%)}**	**{10 Females (83.3%) 2 Males (16.7%)}**	
Age mean ±SD Range	**37.1±12.7 years (14-63) years**	**35.1±13.5 years (14-62) years**	**41.5±10.1 years (29-63) years**	**P= 0.058 NS**
Total No. of sessions	**7.1±3.5 sessions (1-14) sessions**	**8.8±2.9 sessions (5-14) sessions**	**3.4±1.5 sessions (1-7) sessions**	**P= 0.013 S**
Basic platelet count /dl	**32.942±26.282/dl (6.500-91.700)/dl**	**40.930±27.420/dl (12.000-91.700)/dl**	**15.633±11.706/dl (6.500-45.200)/dl**	**P= 0.003 HS**
Basic Hb% in gm/dl	**6.8±1.5 gm/dl (3.9-9.5) gm/dl**	**7.5±1.1 gm/dl (5.4-9.5) gm/dl**	**5.3±1.3 gm/dl (3.9-8.1) gm/dl**	**P= 0.76 NS**
Overall survival	**27 of 38 cases (71.1%)**	**24 of 26 cases (92.3%)**	**3 of 12 cases (25%)**	
Survival in females	**19 of 28 females (67.9**	**17 of 18 females (94.4%)**	**2 of 10 females (20%)**	
Survival in males	**8 of 10 males (80%)**	**7 of 8 males (87.5%)**	**1 of 2 males (50%)**	

Figure 3: Total number of TTP cases, females and males and their total survival rates

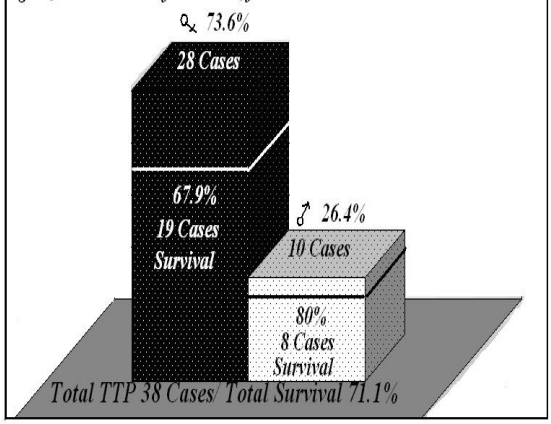


Figure 4: Manifestions related to CNS, renal, fever/sepsis in TTP patients and their survival rates

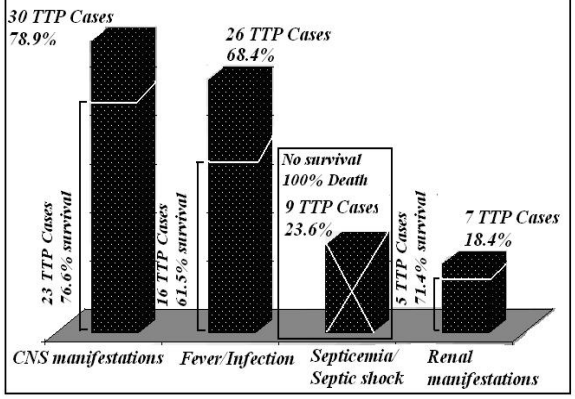
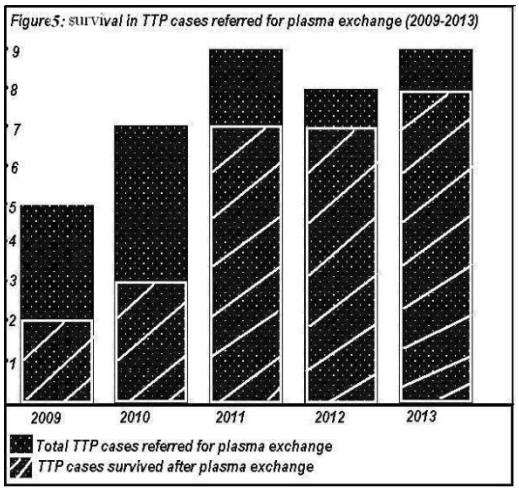


***Table 3*: Survival in TTP cases referred to plasma exchange unit from 2009 to 2013**					
Year	**2009**	**2010**	**2011**	**2012**	**2013**
Total TTP cases	**N=5 13.2%**	**N=7 18.5%**	**N=9 23.6%**	**N=8 21.1%**	**N=9 23.6%**
Survival	**N=2 40%**	**N=3 42.8%**	**N=7 77.7%**	**N=7 87.5%**	**N=8 88.8%**
Total female cases	**N=4 80%**	**N=5 71.4%**	**N=6 66.6%**	**N=6 75%**	**N=7 77.7%**
Survival	**N=1 25%**	**N=2 40%**	**N=5 83.3%**	**N=5 83.3%**	**N=6 85.7%**
Total male cases	**N=1 20%**	**N=2 28.6%**	**N=3 33.4%**	**N=2 25%**	**N=2 22.3%**
Survival	**N=1 100%**	**N=1 50%**	**N=2 66.6%**	**N=2 100%**	**N=2 100%**

Table 4: **Survival in TTP cases referred to plasma exchange unit according to age groups**						
Age	**Less than 20 years**	**21-30 years**	**31-40 years**	**41-50 years**	**51-60 years**	**More than 60 years**
Total TTP cases	**N=4 (10.5%)**	**N=8 (21.3%)**	**N=12 (31.5%)**	**N=7 (18.4%)**	**N=4 (10.5%)**	**N=3 (7.8%)**
Survival	**N=3 75%**	**N=6 75%**	**N=8 66.6%**	**N=5 71.4%**	**N=3 75%**	**N=2 66.6%**



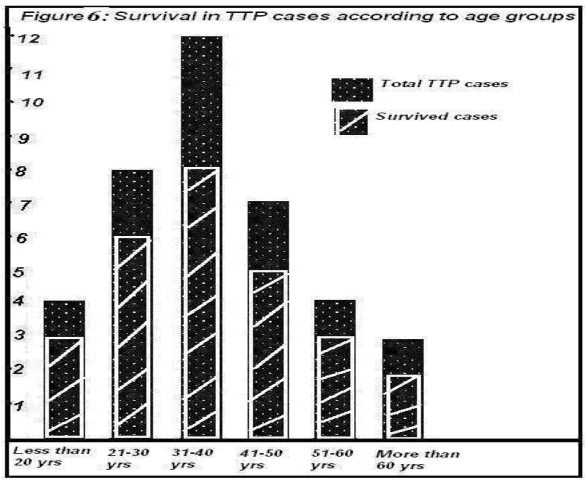
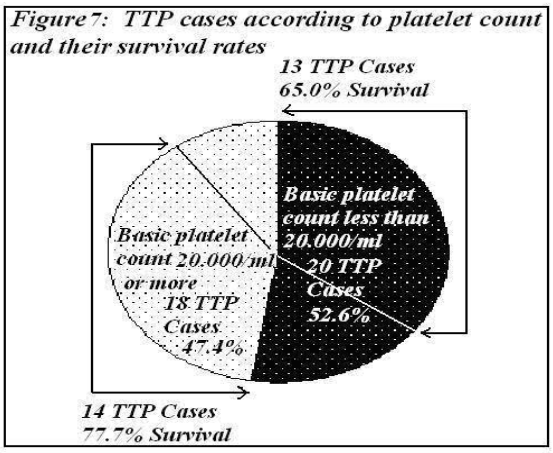
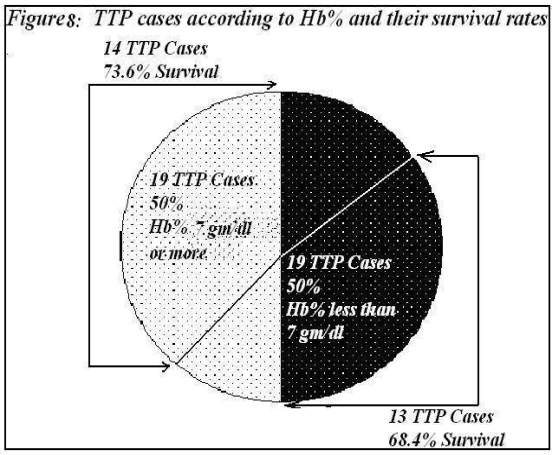


Table 5: **Survival in TTP cases referred to plasma exchange unit according to clinical picture**		
CNS manifestations	**With CNS manifestations N=30 cases (78.9%) Survival=23 cases (76.6%)**	**Without CNS manifestations N=8 cases (21.1%) Survival=4 cases (50%)**
Renal manifestations	**With renal manifestations N=7 cases (18.4%) Survival= 5 cases (71.4%)**	**Without renal manifestations N=31 cases (81.6%) Survival=22 cases (70.9%)**
Fever/infection/ leucocytosis	**With fever/infection/ leucocytosis N=26 cases (68.4%) Survival= 16 cases (61.5%)**	**Without fever/infection/ leucocytosis N=12 cases (31.6%) Survival=11 cases (91.6%)**
	Septicemia/septic shock N=9 cases (23.6%) Survival= none	
Basic platelets count	**Basic platelets count less than 20.000/cc N=20 cases (52.6%) Survival=13 cases (65%)**	**Basic platelets count 20.000/cc or more N=18 cases (47.4%) Survival=14 cases (77.7%)**
Basic Hb%	**Basic Hb% less than 7 gm/dl N=19 cases (50%) Survival=13 cases (68.4%)**	**Basic Hb% 7 gm/dl or more N=19 cases (50%) Survival=14 cases (73.6%)**
Number of plas exchange sessions	**Less than 5 sessions N=10 cases (26.3%) Survival= none**	**5 or more sessions N=28 cases (73.7%) Survival=27 cases (96.4%)**
Removed plasma volur	**One plasma volume N=6 cases (15.7%) Survival= none**	**1.5 Plasma volumes N=32 cases (84.2%) Survival=27 cases (84.3%)**





Discussion

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder. Various centers had made studies as regards the outcome of TTP in patients treated with plasma exchange, plasma infusion or immunosuppressive medications. Our study was a retrospective study including TTP patients referred to Plasma Exchange Unit, Zagazig University Hospitals, Egypt, in the period from 2009-2013, where most of them received combined therapy with plasma exchange (PEX), FFP infusion and corticosteroids. They were diagnosed for having TTP by the presence of microangiopathic hemolysis (MAHA), thrombocytopenia, anemia, with or without CNS manifestations, fever or mild renal manifestations, after exclusion of

other possible causes. We tried to save time and to start therapy as soon as possible for not losing the patients. This is in agreement with the guideline recommendations (1B) ***(17)*** and the revised diagnostic criteria , which state that TTP must be considered in the presence of thrombocytopenia, and MAHA alone and that up to 35% of TTP patients do not have prominent neurological or renal manifestations or fever ***(18) .*** In our study, CNS manifestations were present in 78.9% of patients, renal manifestations in the form of mild renal impairment or proteinuria were present in 18.4% of patients, while infection or fever were present in 68.4% of patients. Whether the infection was the predisposing factor for TTP or a complication to therapy because of IV catheter, IV cannulae , Foley's catheter, or other infections due to immnuo-compromising effect of plasma exchange or corticosteroid was not studied. The etiology or type of TTP was not identified in most patients and the measurement of ADAMTS13 was not done. Daily PEX, preferably with spun apheresis, is the mainstay of treatment of TTP and has reduced mortality rates, from over 90% to 10–20%. It allows removal of autoantibody, and also repletes ADAMTS13. Delay in initiation of PEX leads to preventable early mortality. Although PEX remains the treatment of choice, large volume plasma infusions are indicated if there is to be a delay in arranging PEX. PEX has been shown to be superior to plasma infusion at the end of the first treatment cycle and at 6 months (response rates 47% and 78% vs. 25% and 49%) ***(13).*** In our study, most cases received immediate fresh frozen plasma transfusion (FFP), started pulse steroid therapy and were referred for plasma exchange as soon as possible. We found that the combined therapy, using daily intensive plasma exchange sessions (in most, but not all patients, daily sessions for the first 5 days, followed by every other day sessions, then tapering, but sessions were tailored as required) (till platelet count becomes ≥150.000/cc and then continued for 1-2 more sessions), using a femoral or jugular venous catheter, removing 1.5 plasma volume in each session, adjusted for weight and hematocrit value, using LMWH (20.000-25.000 units) in saline infusion during sessions, replacement with saline 0.9% during sessions, and fresh frozen plasma (FFP) (6-8 units) during the last part of every PEX session and infusion of FFP (2 units) every 8 hours in-between sessions regularly (started immediately after diagnosis of TTP, even before the start of PEX sessions and maintained for a few days after platelet correction to ensure response), together with pulse methylprednisolone (0.5-1.0 gm/day/3-5 days) (started immediately after diagnosis of TTP and given after the session, when PEX is started), followed by oral prednisolone (1-2mg/kg.day) , continued for up to 2 weeks after remission, then tapered, avoidance of sepsis, treatment of infection and frequent changing of intravenous catheter sites, early start of broad spectrum antibiotics, packed RBCs when required, antiepileptic medications for fits, achieved the best results and succeeded in decreasing mortality from TTP and plasma exchange complications**.** In the Canadian apheresis trial, 1·5 plasma volume (PV) exchange was performed on the first 3 d followed by 1·0 PV exchange, thereafter. More intensive exchange, such as twice daily PEX, may be required in resistant cases especially if there are new symptoms such as neurological or cardiac events. The benefit of an intensified PEX regimen has been difficult to document as other treatments are often initiated or intensified simultaneously ***(21).*** Oklahoma TTP registry clarified the impact of secondary causes on mortality, showing a markedly different outcome for idiopathic TTP compared with TTP secondary to 'additional/alternate disorders,' with mortalities of 20% and 58% respectively. Controlling for secondary causes remains important for prognostication even when restricting analysis to specific mechanisms. ***(24).*** Prospective data collected from a clinical trial ***(13)*** showed 4% mortality after the first cycle of plasma exchange, but 22% mortality at 6 months. This difference illustrates the frequency of late deaths and the importance of clearly defining the time at which mortality is measured, which may vary from study to study. Steroids are widely used in combination with PEX in the initial treatment of acute immune TTP. Higher dose pulsed steroids have shown to be associated with an improved patient outcome and usually have minimal side effects. However there is no randomized controlled trial addressing whether a combination of PEX and corticosteroids is superior to PEX alone. Intravenous daily methylprednisolone (e.g. 1 g/d for three consecutive days – adult dose) or high dose oral prednisolone (e.g. 1 mg/kg/d) should be considered (1B) ***(17).*** In our study, we found that high dose pulse steroid, followed by oral steroid, in addition to FFP, had improved the outcome in TTP patients treated with plasma exchange. In our study, 38 cases of TTP were referred for plasma exchange; 28 females (73.6%) and 10 males (26.4%), mean age (37.1±12.7) years, of which only 27 patients (71.1%) survived (19 females and 8 males). Among the 26 TTP patients (Group I) {18 females (69.2%) and 8 males (30.8%)}, who received the combined therapeutic plasma exchange, FFP infusion, and pulse corticosteroids, 24 patients (92.3%) survived (17 of 18 females (94.4%) and 7 of 8 males (87.5%)), while among the 12 TTP patients (Group II) {10 females (83.3%) and 2 males (16.7%)}, in which one or more parts of that protocol were missing, 3 patients (25%) survived (2 of 10 females) (20%) and (1 of 2 males) (50%)). Survival improved from 2009 (40%) to 2013 (88.8%), because of more strict application of the combined protocol. The early suspicion of TTP in any case presenting with thrombocytopenia and anemia, and early examination of peripheral blood film to detect fragmented RBCs and schistocytes had helped in early diagnosis and referral for plasma exchange unit, before serious organ ischemia, thrombosis, or sepsis occur. The availability of FFP for infusion during and in-between sessions was an obstacle for some patients, whose blood groups were not available or the amount of FFP available for replacement was not adequate. Mortality was higher in females and in patients 31-40 years and those more than 60 years. This might be explained by the possibility of secondary causes, which may be more in

middle aged females, in whom autoimmune diseases, pregnancy and use of contraceptives are more common and the suspicion of TTP becomes more delayed because of searching for these causes. The use of platelet transfusion to correct thrombocytopenia, especially when idiopathic thrombocytopenic purpura (ITP) is suspected in young and middle aged females might play a role in the deterioration of their conditions more. Use of azathioprine in one patient , together with oral prednisolone, did not improve outcome, wasted time, delayed the start of plasma exchange and patients had convulsions and sepsis after a few sessions and died. Broad spectrum antibiotics should be started early and maintained, even if patient does not have fever or evidence of infection, because patients become immunocompromised by plasma exchange and steroids and because they usually have intravenous catheter, intravenous cannulae and sometimes a Foley's catheter, which may be sources of infection. The finding of high white blood cell count (WBCs) as an evidence of infection at the start of sessions was associated with worse prognosis in most but not all patients. Replacement with intravenous colloids and human albumin alone (because of unavailability or inadequacy of FFP) was associated with definite mortality. CNS manifestations including confusion, fits or coma showed dramatic improvement after plasma exchange, as long as electrolytes, PH, acid base balance, blood pressure, blood sugar are normalized, no sepsis and no cerebral infarction or hemorrhage, myocardial infarction, pulmonary embolism, GIT hemorrhage or mesenteric vascular occlusion occurred. Omission of one session especially in the first sessions is dangerous, because the first session may be followed by rebound overflow of antibodies into the circulation, which may lead to more thrombocytopenia. The awareness of physicians about the risk of TTP and the importance of its early diagnosis and referral for plasma exchange helped in the diagnosis of more cases at an earlier stage and had improved the outcome of TTP on plasma exchange. The use of plasma exchange alone was not as effective as the combined therapy using FFP infusion after and in-between the sessions and the use of pulse steroid followed by oral steroid. This is in agreement with ***(19)***, where an old female with TTP showed complete remission after being treated with plasma exchange combined with corticosteroids. However, she had to substitute plasma exchange with fresh frozen plasma infusion due to procedure-associated complications. The infusion of fresh frozen plasma was known as less effective and more likely to boost inhibitor titers compared to plasma exchange. The use of FFP regularly every 8 hours before and after the start of plasma exchange was ensured to supply the patients with sufficient ADAMTS13, coagulation factors and to save patients' lives from severe thrombosis or bleeding until plasma exchange becomes available. Cryosupernatant is at least as efficacious as standard fresh frozen plasma (FFP). The UK Department of Health recommends the use of solvent/detergent-treated (S/D) plasma in TTP patients to reduce the risk of transfusion-transmitted infection and adverse immune responses. S/D plasma contains reduced levels of protein S, but an increased thrombotic rate has not been reported in cases where thromboprophylaxis with low molecular weight heparin (LMWH) and low dose aspirin was used routinely once the platelet count was >50.000/cc ***(23).*** In our study, patients were maintained on oral prednisolone for a few weeks, with weekly follow up investigations to exclude relapse or recurrence, followed by tapering and stoppage. Also, we continued to give plasma infusion regularly daily, that was gradually tapered after stopping plasma exchange sessions. We continued plasma exchange for 1-2 sessions after platelet count reached 150.000/cc to make sure of complete recovery. One patient was referred for splenectomy because she had a mild form of relapse, after 6 months oral steroid therapy. The average number of sessions ranged from 1-14 sessions (7.1±3.5). Some patients improved after 5 plasma exchange sessions, in addition to plasma infusion and corticosteroid, while others required up to 14 sessions to improve completely. One patient died after 13 sessions because of serious complications and inadequate plasma infusion or corticosteroid therapy. The duration of PEX and the number of procedures required to achieve remission is highly variable, but is longer in antibody-mediated TTP ***(7).*** In centers which used only plasma exchange ***(12)***, the average number of procedures required for remission was 15·8 (range 3–36). This means that combined therapy reduces the requirement for more PEX sessions and shortens the duration and cost of therapy, with better response. Recovery was marked by disappearance of schistocytes and fragmented RBCs, platelet count of more than 150.000 for 3 days, return of reticulocytic count, total and indirect bilirubin, LDH, increased hemoglobin to 9 gm / dl and absence of elevated WBCs, sepsis, convulsions, renal impairment, confusion, fits, hemorrhage, thrombosis or fever. The color of removed plasma was also an indicator for the response and the absence of hemolysis. Better and faster response occurred when we started plasma exchange early, before patients' hemodynamics deteriorate, and this allowed exchange of 1.5 volume, corrected according to hemtocrit value automatically by the machine through patients' body weight and hematocrit value. Delay in FFP infusion, start of pulse steroid or start of plasma exchange deteriorates patient's hemodynamics and makes sessions more risky and the plasma volume removed to be reduced, which causes patient's loss. When patients were at risk for bleeding because of very low platelet count and the use of heparin during plasma exchange sessions, we used to give proton pump inhibitors and start plasma infusion early during the session. We did not use aspirin, dipyridamole, cyclosporine or rituximab. We did not test for the level of ADAMTS13 activity because it was not available at our hospital. Complicated and risky TTP patients should not be managed in ward but in ICU, because they may look in a good condition, when they suddenly deteriorate (even after initial response to therapy), develop coma, fits, bleeding, cardiac arrest, pulmonary emboli or septic shock. They should be managed carefully till their laboratory data become normal. Postponing, delaying or

premature stoppage of plasma exchange may lead to catastrophe due to sudden release of more antibodies, especially if plasma removal was not enough and patient was not on steroid therapy or FFP infusion. Daily exchanges should continue for a minimum of 2 d after complete remission, defined as normal platelet count (>150.000/cc). This is in contrast to other studies ***(22),*** who found that tapering (reducing frequency and/or volume of PEX) has not been shown to reduce relapse rates. TTP is one of the most critical and risky conditions that are met with in the plasma exchange units and should have the priority for sessions in a daily working unit. Correction of electrolytes, fluid and acid base balance is mandatory. Ensuring good oxygenation to all body organs is needed. Stopping any offending medications is important. The possibility of heparin-induced thrombocytopenia, alternative diagnosis, relapse or failure of response or the presence of critical secondary cause should be kept in mind. In TTP with malignancy, plasma exchange has no benefit and the treatment of the underlying cancer is the mainstay of therapy ***(21).*** Follow up laboratory investigations should be done daily, if possible. Pulse steroid should be followed by a full dose of oral steroid, then gradual tapering according to the condition. Referral for splenectomy or other measures is advised if no response after several sessions or if there is a relapse. Randomized clinical trials conducted by the Canadian Apheresis Group showed that the following variables predicted mortality: age $\geq$ 40 years, hemoglobin $\leq$ 9.0 g/dl and presence of fever $\geq$ 38.5 C, with the presence of neurologic abnormalities were no longer predictive of mortality after adjustment. Earlier studies showed that the presence of stupor or coma was highly predictive of mortality, but this discrepancy may be related to the consideration of less severe findings, including focal deficits, confusion, and behavioral changes ***(20).*** In our study, we found that survival was lower in TTP patients included: age 31-40 years or more than 60 years, female gender, the presence of fever, infection or leucocytosis, basic platelets count less than 20.000/cc, PEX sessions less than 5 sessions, inadequate plasma volume removal, delay of therapy, and inadequate FFP or steroid.

Conclusion

Better outcome in TTP patients could be achieved through: Early suspicion, early diagnosis, early FFP infusion, early start of pulse steroid, followed by oral steroid, with broad spectrum antibiotics to avoid sepsis, early referral for plasma exchange unit, daily 1.5 plasma removal for 5 successive days,

then every other day sessions, then tapering, with FFP infusion at the end of each session and in-between sessions. Admit to ICU especially at the first days of therapy and if patients are unstable. Search for secondary causes of TTP, if required or consider other causes for MAHA.

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