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# The Role of Aspirin in Thrombotic Thrombocytopenic Purpura: A Randomized Control Trial

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**Objective: To assess the safety and efficacy of aspirin in acute Thrombotic Thrombocytopenic Purpura (TTP) and to evaluate it as a maintenance therapy.**

**Design: Randomized controlled trial.**

**Setting: Hematology/Oncology Department, Salmaniya Medical Complex (SMC), Kingdom of Bahrain.**

**Method: Nine patients with TTP admitted between August 2003 to December 2005 were included in the study. Seven were females (77.8%) and one was pregnant. Five Patients were randomized to receive the standard therapy with aspirin (group I) and four (group II/control) received the standard therapy only (plasma exchange, one single plasma volume daily using fresh frozen plasma from healthy donors and Methylprednisolone 1 gram intravenously once daily for three days). Safety and efficacy of aspirin were assessed during the acute phase (4 weeks) and as maintenance for one year.**

**Result: Statistically significant reduction in the number of plasma exchange sessions were noted in the aspirin group (*p = 0.0315*). Other parameters such as days of hospitalization, red blood cells transfusion were lower in the aspirin group compared to non aspirin group. No cases of mortality or morbidity were observed in patients receiving aspirin. Two patients (50%) developed deep vein thrombosis (DVT) in the control group and one of them eventually died (25%). Though these were statistically insignificant, possibly due to the small number of patients, it would suggest the efficacy of aspirin in TTP.**

**Conclusion: The study showed a significant reduction in the number of plasma exchange sessions in the aspirin group and probable advantages. Accordingly, we recommend a multicenter RCTs to address the role of aspirin in the management of TTP patients.**

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Thrombotic thrombocytopenic purpura (TTP) is a rare hematologic disorder with an incidence of 3-4 patients/million/year[1]. The main pathological feature of TTP is microvascular platelet thrombosis manifesting as thrombocytopenic purpura, microangiopathic hemolytic anemia, fever, renal involvement and fluctuating neuropsychological signs and symptoms[1,2].

The prognosis of TTP was mostly lethal until late 1970s[1,3]. The introduction of plasma exchange techniques, had markedly improved the survival[1,3]. Currently, plasma exchange is the primary standard therapy for TTP[1-3]. Several drugs such as steroids and immunoglobulins have been added to the treatment protocols[4]. Moreover, antiplatelet agents are often included in plasma exchange regimens for TTP patients, though their use is still controversial, mainly due to the fear of inducing or augmenting bleeding[1,2,4].

The aim of this study was to evaluate the role of aspirin in TTP.

**METHOD**

Nine patients diagnosed as TTP admitted to Hematology/Oncology unit from August 2003 to December 2005 were included in the treatment protocol. Two were males (22.2%), seven were females (77.8%) and one was pregnant.

The diagnosis of TTP was based on the presence of the following: thrombocytopenia (platelet count less than $100x10^9$/L), microangiopathic hemolytic anemia [with schistocytes in peripheral blood smears, high Lactate Dehydrogenase (LDH) and high indirect bilirubin] and no other possible causes of anemia and thrombocytopenia. Informed consent was obtained. The local ethical research committee approved the study.

Nine patients with a diagnosis of TTP were treated with the standard protocol: plasma exchange, one single plasma volume daily using fresh frozen plasma from healthy donors and Methylprednisolone 1 gram intravenously once daily for three days. If platelets counts were greater or equal to $50 \times 10^9$/L, the patients were openly randomized to either group. Five patients received low dose aspirin of 81 mg once daily and continued for one year. Four patients received the standard therapy and were considered the control group. The number and volume of plasma exchanges, additional packed red cell transfusions, salvage therapy with Vincristine, days of hospitalization and complications related to TTP were verified to investigate the effectiveness of aspirin. The patients were followed for a year and observed for early and late relapses. All complications or episodes of bleeding were reviewed to assess the safety profile of aspirin. Figure 1 shows summary of the flow of participants through each stage of the randomized trial.

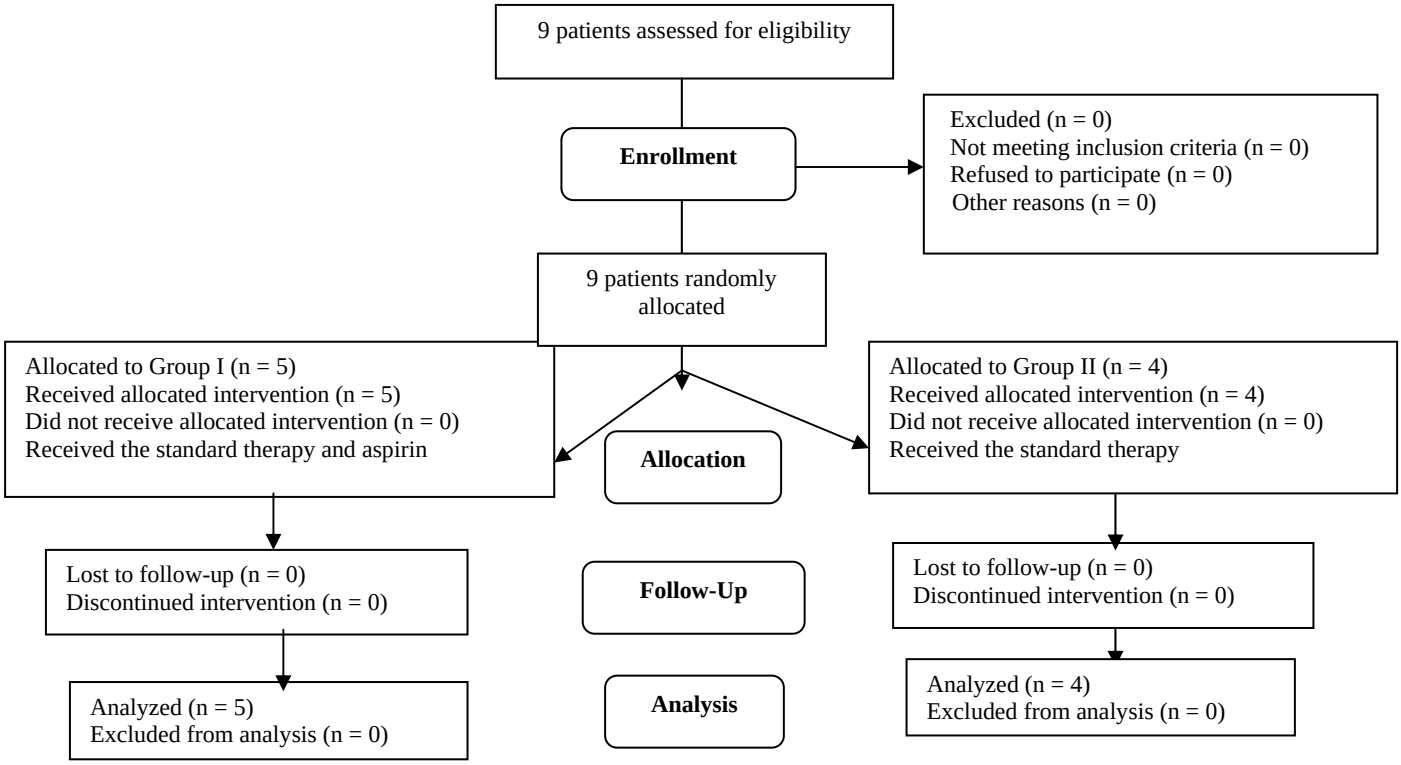


**Figure 1: Randomization of Aspirin in Thrombotic Thrombocytopenic Purpura**

Nine patients diagnosed as TTP were treated at SMC during the study period were included, provided that their platelets count was greater or equal to 50 x $10^9$/L after the standard protocol and no overt significant bleeding.

No patient was excluded because none of them met the criteria for exclusion that is less than 50 x $10^9$/L after the standard protocol, or with overt significant bleeding or having contraindication to aspirin therapy e.g. peptic ulcer disease.

SPSS program version 17 was used for statistical analysis. A time limit for the study was selected due to the rarity of the disease. The results were calculated using chi-square and T-tests.

## RESULT

Nine patients were included in the study, two were males (22.2%), seven were females (77.8%) and one was pregnant. The patients were randomized to either aspirin (group I) or no aspirin (group II). Five patients received aspirin, the mean age was 29 years (range 19-46 years). Four patients were randomized to group II; the mean age was 40.8 years (range 32-52 years).

Clinically, all patients presented with thrombocytopenia (mean platelet count of 21.3 x $10^9$/L, a range of 5-45 x $10^9$/L), microangiopathic hemolytic anemia with schistocytes in the peripheral

smear (mean hemoglobin level of 7.52 g/dL and of range: 5.8 - 9.9 g/dL). None of the patients had bleeding upon enrolment; three had sickle cell disease (SCD), two of them had acute chest syndrome, one in each group. One patient had convulsion at presentation while the third SCD patient had multiple cerebral infarcts, see Table 1 and Table 2.

**Table 1: Personal and Biohumoral Data**

| | Overall mean | Group I mean | Group II mean | p value |
|---|---|---|---|---|
| Age range (years) (Mean) | 34.2 | 19-46 (29.0) | 32- 52 (40.8) | NS [a] |
| Number of patients | | 5 | 4 | NS [a] |
| Sex Male (%) | | 1 (20%) | 1 (25%) | NS [a] |
| Female (%) | | 4 (80%) | 3 (75%) | |
| Pregnant | | 1 (20%) | 0 (0%) | NS [a] |
| Platelets (RR [b] 150-400 x$10^9$/L) | 21.3 | 11 | 34.25 | NS [a] |
| Hemoglobin (RR [b] 11-17 g/dL) | 7.52 | 7.52 | 8.025 | NS [a] |
| LDH (RR [b] 100-190 U/L) | 1772.7 | 1561.4 | 2037 | NS [a] |
| Urea (RR [b] 3-7 mmol/L) | 8.4 | 6.5 | 10.3 | NS [a] |
| Creatinine ( RR [b] 60-140umol/L) | 135.08 | 131.4 | 138.75 | NS [a] |
| Indirect Bilirubin (RR [b] less than 18 umol/L) | 21.43 | 23.22 | 19.63 | NS [a] |

[a] NS = not significant, [b] RR = reference range

**Table 2: Clinical Features**

| Features | Group I | | Group II | | p value |
|---|---|---|---|---|---|
| | No | (%) | No | (%) | |
| Bleeding | 0 | 0 | 0 | 0 | N.S. [a] |
| Convulsion | 0 | 0 | 1 | 25 | N.S. [a] |
| Fever | 3 | 60 | 1 | 25 | N.S. [a] |
| Renal | 1 | 20 | 1 | 25 | N.S. [a] |
| Hepatosplenomegaly | 1 | 20 | 1 | 25 | N.S. [a] |
| SCD [b] | 1 | 20 | 2 | 50 | N.S. [a] |

[a] NS = not significant
[b] SCD = sickle cell disease

There was statistical significant reduction in the total number of plasma exchanges sessions in favor of Group I ($p < 0.0315$). The mean number of plasma exchanges session in group I was 3.6 (+/- 3.04 SD) and 8.75 (+/- 3.5SD) in group II.

The mean of the hospitalization days was 13 days (+/- 9 SD) for group I compared to 25 days (+/- 12.1 SD) for group II. The mean number of red blood cell transfusion was 0.4 units for group I compared to the mean of 3.25 units in group II. The mean plasma exchange volume in aspirin group I was 8964 cc (+/- 7320 SD) compared to 18672 cc (+/- 8157.2 SD) in non aspirin group II.

Two patients (50%) of the non aspirin group developed deep vein thrombosis (DVT) and eventually one (25%) died. None of the patients had bleeding episodes after aspirin. None of the patients declined the treatment in the acute phase or in the maintenance phase.

Eight patients (88%) of the treated patients attained clinical remission irrespective of their assigned group. One (11%), assigned to non aspirin arm, failed to respond and eventually died. Five patients (100%) in aspirin group achieved clinical remission compared to three (75%) of the non aspirin group. Moreover, the remission was attainable by using plasma exchange and Methylprednisolone at the initial phase, followed by aspirin as per assigned group and lastly by salvage therapy such as Vincristine. Two patients (40%) of the treatment group and one patient (25%) of the control group achieved complete remission with Vincristine.

Once complete remission achieved, aspirin patients were instructed to continue on the low dose aspirin as a maintenance therapy for one year; the other group did not receive aspirin. Both groups were followed up after the study period. No cases of early or late relapse were noted in either group during the study period. However, there were two cases (25%) of relapse, one in each group beyond the study period; one patient in the control group (33.3%) relapsed after 2 years, while another patient in aspirin group (20%) relapsed after 3 years, see Table 3.

**Table 3: Outcomes of both Groups**

| Outcomes | Group I | Group II | p value |
|---|---|---|---|
| Days of Hospitalization (Mean) | 3-29 (13.8) | 17-43 (25) | NS [a] |
| Total number of plasma exchange (Mean) | 18 (3.6) | 35 (8.75) | 0.0315 |
| Total Volume of plasma (ml) (Mean) | 44820 (8964) | 74690 (18672.5) | NS [a] |
| Salvage treatment (VCR) [b] | 2 patients 40% | 1 patient 20% | NS. [a] |
| Transfusion of PRBC [c] (units) (mean) | 2 (0.4) | 13 (3.25) | NS [a] |
| Complications (%) | 0 0% | DVT (2 cases) 50% | NS. [a] |
| Recurrence (%) | 1 (after 3 yrs) 20% | 1 (after 2 yrs.) 25% | NS [a] |
| Death (%) | 0 0% | 1 25% | NS [a] |

[a] NS = not significant, [b] VCR = Vincristine, [c] PRBC = packed red blood cells

## DISCUSSION

TTP is a hematological emergency characterized by thrombocytopenia and microangiopathic hemolytic anemia without an apparent cause[1,5]. The classical five clinical features are not often evident and early diagnosis with rapid initiation of treatment is important in the management of this fatal condition[1-3,5].

The discovery of the von Willebrand factor cleaving protease (VWF-CP), also known as ADAMTS13, has contributed to the recognition of the pathogenesis of TTP[1,5]. The platelet aggregation is due to the deficiency of the ADAMTS13 factor resulting in accumulation of very-high- molecular- weight von Willebrand factors (HMW-VWF) multimers, thus causing platelet microthrombi[1,5]. Measurement of ADAMTS13 activity is not necessary for the diagnosis[5].

The disease was almost fatal until late seventies. However, with the introduction of plasma exchange, the outcome of TTP has dramatically improved and survival rates increased from 10 to 90%[1-3,5]. Plasma exchange removes HMW-VWF multimers and infuses normal plasma, which replenish the missing VWF-CP[1,5].

Most cases of TTP respond well to plasma exchange regimes. However, few cases do not achieve complete remission. Thus, other therapies have been tried. Vincristine has been used producing promising results. Nonetheless, it is a cytotoxic drug with several serious complications[6]. Steroids have been tried with varying responses, and currently considered by many centers as a part of their initial standard protocol along with plasma exchange for TTP management. Again, it is not without side effects and failure[1,5,7-9].

The main pathological feature in TTP is platelets microthrombi, and antiplatelet agents are well known to inhibit platelets aggregation by producing irreversible inhibition of prostaglandin production; therefore, antiplatelet drugs have been used by many centers with variable degree of responses[1-13]. However, their use is still controversial due to induction or augmenting bleeding[1,2,4]. Rosove et al concluded that aspirin and Dipyridamole are ineffective in TTP and may cause serious bleeding complications[11]. This could be due to large doses of aspirin combined with Dipyridamole. Bell et al reported that five patients in their case series did not respond to aspirin and Dipyridamole combination[12]. However, aspirin was used in very severe cases resistant to aggressive treatment of plasma exchange and steroids[12].

Our sample size was small because TTP is an uncommon disease. Aspirin 81 mg was used in our study because low dose aspirin is effective and avoids the side effects of the drug, mainly bleeding[4,7]. In previous studies, the risk of bleeding was a concern against the use of antiplatelet therapy[4,11]. However, we have not faced any bleeding, and the use of aspirin even in severe thrombocytopenia is considered safe by many centers[8].

In this study, patients who received aspirin had fewer plasma exchanges compared to patients who received the standard therapy, also they had fewer days of hospitalization. All patients in the aspirin group achieved clinical remission compared to 75% of the non aspirin group. Few studies have used higher doses of aspirin regardless of the severity of thrombocytopenia[3,7].

Furthermore, aspirin group had less need for supportive RBC transfusions compared to non aspirin group. It appears that aspirin is safe in acute TTP as none of the patients experienced any bleeding episodes nor developed serious side effects attributed to aspirin.

In group II, one patient developed DVT and eventually died. DVT is a complication of TTP. In a study by Bobbio et al, five deaths in non aspirin group compared to one death in aspirin group[7].

In this study, one patient in each group had relapsed but after more than one year. The patients in the aspirin group relapsed three years after discontinuing aspirin. It might be worthwhile to consider maintenance therapy for longer than 12 months to prevent late relapses. Similarly, Myers et al reported that anti platelets agents, similar to aspirin, have positive effect in remission induction and preventing relapses[2].

In a recent systemic review of RCTs studies, addressing different interventions for TTP, Michael et al concluded that plasma exchange remains the primary intervention for patients with TTP. Alternative therapies grant no additional benefit[5]. Although, in their review, they found only one RCT study by Bobbio et al, which showed a significant benefit of aspirin in maintenance and apparent benefit in the acute phase of TTP and advocated its use[5,7].

## CONCLUSION

**Although the number of patients in this study was small to draw definite conclusions, aspirin significantly decreased the numbers of plasma exchanges.**

**Aspirin is safe to use; accordingly, we recommend the use of low dose during the recovery of the acute TTP when platelets counts are greater or equal to 50 x $10^9$/L and as a maintenance therapy.**

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