Management of Symptomatic Thrombocytopenia Associated with Dengue Haemorrhagic Fever

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Introduction: Immune – mediated destruction of platelets is thought to be the mechanism of thrombocytopenia seen after the viraemic phase of dengue haemorrhagic fever (DHF). Immuno – suppressants such as steroids, immune globulin and Anti D immuneglobulin are effective in the treatment of this type of immune thrombocytopenic purpura.

Objective: To evaluate the efficacy of oral Prednisolone in the rate of resolution of thrombocytopenia and monitoring of complications in patients recovering from Dengue haemorrhagic fever.

Method: A controlled study was carried out on diagnosed cases Dengue haemorrhagic patients presenting with sever thrombocytopenia and symptoms like confluent ecchymosis, epistaxis and purpuric rashes. In study was conducted in Ittefaq hospital (trust) Lahore, during the period of October to December 2008. Treatment group received steroids in two forms i.e. 1st line therapy prednisolone (1 mg / kg) orally or as 2nd line therapy of initial I/V high dose (prednisolone) in pulse doses i.e. 40 mg / bd for four days and later oral prednisolone as in 1st line therapy with omeprazole 20 mg / bd in addition to standard treatment. Control group received standard supportive care only.

Results: A total of **341** suspected patients were admitted in hospital. Serological diagnosis was confirmed in 166 patients. CBC revealed platelet count $\leq 100 \times 10^9$ / l in 106 patients. A group of symptomatic febrile patients have platelet count $< 20 \times 10^9$ / l was selected for therapeutic intervention. 1st line therapy (oral prednisolone was stated in 43 patients. In Fourteen patients 2nd line therapy (high dose dexamethasone pulse) therapy was instituted. Seven of them attained complete response whereas two patients achieved partial response. Four patients were shifted to Anti D therapy. Three deaths occurred during our study. Rest of all the patients improved and were discharged in due course of time.

Conclusion: This small scale preliminary study shows promising results in reducing the morbidity of patients in a relatively serious stage but large scale double blinded randomized controlled studies are needed before making recommendations on use of steroids in symptomatic thrombocytopenic patients with dengue haemorrhagic fever.

Introduction

Dengue viral infection in humans presents mostly as Dengue fever (DF) or dengue hemorrhagic fever (DHF). Dengue virus types 1 – 4 induce a wide spectrum of clinical presentations including hemorrhagic manifestations associated with thrombocytopenia and increased vascular permeability.[1] Thrombocytopenia is a common problem in dengue which causes concern for the patients and treating doctors.[2] The pathogenesis of thrombocytopenia in dengue fever is not clearly understood. Increased peripheral destruction of antibody coated platelets is strongly suspected as the possible mechanism. Other modes include acute bone marrow bone suppression leading to amegakaryocytic condition and enhanced platelet destruction by the reticuloendothelial system.[3]

The tendency by the clinicians to transfuse platelet rich plasma (PRP) is quiet natural while managing a patient having complications due to thrombocytopenia.[3] However, platelets present a strong antigenic stimulus, which by evoking an exalted immune response, could cause further immune mediated platelet destruction. Consequently, platelet counts of dengue patients fluctuate in an unpredictable manner despite platelet transfusion. Platelet rich plasma is costly, needs specialized skills and machinery, and can be stored for only a few hours.[4]

Various treatment options are presently available including Prednisolone, high dose Intravenous immunoglobulin, intravenous administration of anti – D (rh_0 – d), Immune globulin and transfusions of platelet concentrates and Fresh Frozen Plasma.[3,5] All these options are valuable in different clinical situations. We used various treatment protocols in different patients according to response and stage of disease.

Material and Methods

A total 341 suspected cases of dengue fever were admitted in Ittefaq Hospital (trust) Lahore during the epidemic i.e. 22nd October to 4th December 2008. All the patients were subjected to serological tests including antibody detection of dengue specific IgM and IgG with ELISA technique.[6]

All the confirmed patients of Dengue viral infection underwent detailed of clinical examination and haematological findings in the patients were recorded. Patients were examined at least once daily during their stay in the hospital. For monitoring purposes 03 cc of blood samples were drawn in EDTA for CBC at the time of admission and on alternate day during acute phase. In convalescent stage samples

were taken on every third day. Complete Blood count (CBC) was carried out in auto cell analyzers i.e. Sysmex XT 1800i / KX 21. Platelet counts were recorded in each individual and the results were verified on slide. Each determination was done in duplicate at the time of admission, days 7 and 10.

Out of 341 acute cases, 166 (48.7%) were confirmed by using dengue specific IgM, Among these 166 case, (44) 18% were labeled as DHF cases on the basis of IgM +ve, TLC < 3.0, Platelets < 100. None of these patients showed sign and symptoms of Dengue shock syndrome (DSS) like hypotension, shock etc during their illness or hospital stay. Male to female ratio was (1 : 0.8) and child to adult ratio observed was (1:4.5).

Results of blood samples drawn for CBC on the day of admission were recorded. In 106 (66.25%) patients the platelet counts were 100×10^9 / l or below.

Out of 106 thrombocytopenic patents, 57 had clinical symptoms such as multiple bruises, ecchymosis epistaxis. These patients were transfused platelet transfusions either random donor or mega units collected by plasmapheresis. The selection of platelet was random and availability/ non-availability of the donor for plasmaphereis was the major deciding factor for the type of platelet transfusion. The symptomatic patients having platelet count < 10×10^9/l received prophylactic platelet transfusion till their recovery from severe thrombocytopenic state.

For immunosuppression most patients were treated according to the following algorithm.

First – Line Treatment: This consisted of oral Prednisone (1 mg / kg / d) for 3 to 6 weeks, followed by a tapering off according to the response. Intravenous preparations were considered only in those patients where clinical conditions did not allow oral ingestion. Other treatment options were considered when no platelet response was seen after at least 3 weeks of prednisone, one or more recurrences after withdrawal of prednisone, or requirement of maintenance prednisone treatment.

Second – Line Treatment: High dose Dexamethasone in pulse therapy: Intravenous administration of Depomedral (Methyprednisolone) at the dose of 40 mg twice daily over a period of several minutes for 04 days Criteria for repeat infusions was mainly lack of proper response i.e. a platelet count less than 20 to 30×10^3/µl.

Third – Line Treatment: Anti – D (Rh_0 – D) immune globulin was administered at a dose of 250 IU / kg (50 µg / kg) as daily infusions for 4 to 5 days subsequently; treatment consisted of a single administration.

Response Criteria: Complete response was defined as a platelet count of more than 100.0×10^9 / l without therapy. Partial response was defined as a platelet count >30.0×10^9/l but less than 100.0×10^9 / l. Response to maintenance therapy was defined as a platelet count of more than 30.0×10^9 / l during drug therapy. No response was defined as a platelet count of less than 30.0×10^9 / L with or without therapy.

Results

The 57 patients presenting with counts below 100×10^9 / l had clinical symptoms such as multiple bruises, ecchymosis and epistaxis. Treatment was instituted according to the clinical presentation of the patients. Out of 57 patients, treatment was started in 43 patients. The criteria of starting immunosuppressive treatment was severe thrombocytopenia (platelets < 20×10^9 / l) in presence of febrile spike and presence of clinical symptoms. In a small subgroup of 14 patients intravenous high dose Dexamethasone pulse therapy was instituted for a period of 04 days due to severity of disease i.e. confluent ecchymosis and massive epistaxis, and then shifted to oral prednisone. Two patients were put on Anti – D (Rh_0 – D) immune globulin.

Table 1: *Clinical presentation of hospitalised patients with DHF.*

Clinical Features	No of cases / (%)
Fever	57 (100%)
Headache	45 (80.5%)
Arthralgia	37 (65.0%)
Vomiting	94 (62.7%)
Myalgia	100 (66.7%)
Abdominal pain	29 (51%)
Retro-orbital pain	20 (35.5%)
Sore throat	19 (33.0%)

Table 2: *Bleeding manifestations in patients of dengue hemorrhagic fever.*

Site of Bleeding Frequency	
Major Symptoms	**Frequency**
Gum bleeds	11 (19.2%)
Patechiae	57 (100%)
Menorrhagia	9 (15.7%)
Ecchymosis	38 (66.6%)
Epistaxis	10 (17.5%
Haematemesis	3 (5.2%)
Melaena	5 (8.7%)

Baseline characteristics of all our patients with the main presentation of severe thrombocytopenia are shown in Table 1 and 2. The mean age at diagnosis was 34 years with the male : female ratio 34 : 23.

Three patients with severe thrombocytopenia at diagnosis died during the first three days of starting the treat-

ment. A 25 – year – old woman, with a platelet count of 3.0×10^9 / l died from intra–cerebral bleeding. A 65 – year – old woman, with a platelet count of 11×10^9/l before death, died due to massive GI bleed. A 24 – year – old boy, with a platelet count of 1.6×10^9 / l before death, died due to massive intracranial bleed.

Haematologic Response: Of 14 patients with severe thrombocytopenia, 07 attained a complete response and 02, a partial response on high dose Dexamethasone pulse therapy. First – line therapy contributed to 20 of these 29 responses. Half of the patients with severe thrombocytopenia, who attained a complete response on prednisone showed initial response within one week of start of therapy. Two patients who did not respond even on 2nd line therapy were put on intravenous Anti D immune globulin. Both the patients showed moderate recovery and became symptomless within 24 hours of starting the regimen. None of the patients with initial response showed clinical deterioration or experienced bleeding complications during follow-up.

Discussion

There is strong evidence that the thrombocytopenia and skin – mucosal bleeding in dengue viral infections is due to activation of immune process and direct marrow suppression by the viral particles.[6] Thrombocytopenia and related clinical presentations associated with viral infection seems to result both from a reduction in the production of platelets from Megakaryocytes and from a decrease in the half life of the platelets.[7] Platelets are sensitized by auto antibodies and then are destroyed by cells of the reticulo – endothelial system, particularly those of he spleen. These auto antibodies against glycoproteins of the platelet membrane can be identified in 80% of the patients.[8]

The main objective in treating severe thrombocytopenia is to achieve stabilization of the platelet count at a level that would prevent a major risk of bleeding.[9] Many authors have suggested that it is important to avoid unnecessary treatment of asymptomatic patients with moderate thrombocytopenia. Moreover, the efficacy of the therapy is uncertain among asymptomatic patients with severe thrombocytopenia. Such patients have reported that the morbidity related to the side–effects exceeds the problems caused by the disease itself.[10]

Thrombocytopenia generally requires careful monitoring of the clinical presentation and in majority or cases active treatment is not required till the counts are very low (below 20×10^9 / l) in the presence of febrile spikes.[10,11] The preferred line of treatment is using oral prednisone at pharmacologically effective dose of 1 mg / kg / day.[12] Most patients with severe thrombocytopenia generally show a positive response to prednisone within two weeks of starting the treatment. In case the patient remain symptomatic or continue having platelet counts $< 10 \times 10^9$ / l then he would be the candidate for second line treatment.[13]

In the present series of post dengue thrombocytopenia, no platelet count record could be traced before the disease. However, considering this to be a primary case of infection by the dengue virus, the perpetuation of the low platelet count probably occurred through immunological mechanisms, thus characterizing a condition of post-dengue ITP.[14]

There is strong evidence that corticosteroids act in a duel way. At one hand there is increased production of platelets in the bone marrow by direct activation of Megakaryocytes and in second place the clearance of dengue virus from the bone marrow is enhanced by suppressing the unwanted production of auto antibodies in the immune system.[15]

Kularatne and colleagues have shown in a randomized controlled study that a short course of Dexamethasone in dengue fever during febrile thrombocytopenia shows a significant benefit in increasing platelet count. As the mechanism of thrombocytopenia in febrile phase is mainly through immunological bone marrow suppression by the virus, these results are more enhanced during the defervescence.[16]

The main limitation to our study is the small sample size but with increasing experience we would be in a position to deal with all relevant problems in a better way.

Conclusions

Its is not easy to draw conclusion from such a small scale study but current evidence suggests that steroids can be effectively used as Ist line therapy in clinical situations where the morbidity and mortality depends on timely decision of the clinician. Lot of effective therapies such as intravenous immunoglobulin and Anti D trials are available but the main factor in our set up is the affordability of patients for these expensive medicines.

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