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Research Article

A prospective observational study of dengue fever with thrombocytopenia with reference to treatment

Shashidhara Kuppegala Chikkaveeraiah*, Rajashekar Reddy, Arun Kumar

Department of Medicine, J.S.S Medical College, JSS University, Ramanuja Road, Mysore-570004, Karnataka, India

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***Correspondence:**
Dr. Shashidhara Kuppegala Chikkaveeraiah,
E-mail: kcshashidhara@gmail.com

ABSTRACT

Background: Dengue fever is treated according to the WHO guidelines worldwide but due to the unavailability of blood products and economic constraints treating physicians often modify according to the patients requirements and try to give best available treatment for the patients. So we did an observational study of dengue fever and evaluated the clinical profiles and prognosis of dengue fever with reference to the treatment in JSS Medical College, Mysore in south India, a tertiary medical centre.
Methods: This two year prospective, observational study was conducted in JSS Medical College. A total of 128 patients were evaluated and were divided into three groups like group 1-mild risk, group 2-moderate risk and group 3-high risk depending on the platelet count levels and bleeding diathesis. Group 1 received supportive treatment, group 2 received supportive treatment and steroids (Inj dexamethasone 4mg IV q8h) and group 3 received supportive treatment with steroids and platelet transfusion. Clinical evaluation and relevant investigations like blood culture; malarial parasites and febrile serology (acute and convalescent) were performed.
Results: This observational study revealed that dengue fever can be managed symptomatically according WHO guidelines and platelet transfusion is done only when platelet count is less than 10000/cumm or in bleeding diathesis irrespective of platelet count.
Conclusions: Steroid usage alone or along with platelet transfusion had no effect on the platelet count or on the overall outcome of the patient.

Keywords: Dengue haemorrhagic fever (DHF), Dengue shock syndrome (DSS), Thrombocytopenia, Fever

INTRODUCTION

Dengue infection is the most common mosquito-borne viral disease in the world and around 50 million dengue infections occur each year.[1] In South-East Asian region the case fatality rates are 1%, but in Myanmar, India and Indonesia reported rates of 3%-5%.[1]

In dengue fever (DF) the pathogenesis of Thrombocytopenia is poorly understood. The possible mechanism explained is an enhanced peripheral destruction of antibody coated platelets. Other mechanisms are acute bone marrow suppression leading to a megakaryocytic condition and increased destruction of platelets by the reticuloendothelial system.[2,3]

Dengue fever causes thrombocytopenia commonly which often leads to life threatening complications like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Both are fatal complications leading to hemorrhagic diathesis and circulatory collapse.[4,5] Global attempts have been made to develop new treatment strategies to combat these fatal complications of dengue.[6] There are limited studies in the literature assessing benefits and risk of different modalities of therapy in thrombocytopenia in dengue infection. Various regimens

have been used and some of them have shown beneficial effects and some without benefits.

One of the studies has revealed that World Health Organization (WHO) guidelines were followed by only 16 (45%) physicians and 6 (40%) pediatricians in the management of DF and DHF and steroids and platelets are used empirically in anticipation of bleeding diathesis.[5]

In acute dengue fever with thrombocytopenia platelet transfusion were given empirically in the anticipation of bleeding diathesis leading to treatment with over use of corticosteroids, intravenous immunoglobulin[7,8] and platelet transfusion.[9,10] In hospitalized patients with dengue in Taiwan.[10].

Around 50.3% and in Singapore around 12.6% patients received Platelet transfusion.[9]

Corticosteroids have got wide range of effects on immunological processes including their potent anti-inflammatory effects. In WHO guidelines corticosteroids are not mentioned in the management of dengue but clinicians in south East Asian countries empirically use corticosteroids based on the possible immunological basis of the complications of dengue.[5]

Corticosteroids are effective for stabilizing capillary permeability and have been used in addition to fluid replacement.[5] Many trials compared intravenous hydrocortisone hemisuccinate with no corticosteroids or placebo[6,11,12] and one compared methyl prednisolone with placebo.[13]

Futrakul et al showed a positive response with high dose of methyl prednisolone with mannitol in severe DSS unresponsive to fluid replacement.[14] In spite of these uncertainties steroids are still used in dengue infection by local clinicians in Srilanka.[5] However cochrane reviews concluded that there is insufficient evidence for the use of steroid in DSS and DHF and advised for large randomized trials.[7]

Platelet transfusion carries a variety of risks including viral, bacterial and parasitic infections, allergic reactions, and febrile non-hemolytic reactions alloimmunisation with resulting refractoriness; transfusion associated acute lung injury.

There are data in various institutions for the indications for platelet transfusion. Kumar et al in his study has shown 56.2% inappropriate platelet transfusion during dengue Delhi epidemic in 1999. In dengue fever with thrombocytopenia platelet transfusion is given because of the patient relative's social pressure on treating physician rather than the medical indication.[15-18]

In dengue fever prophylactic platelet transfusions increases platelets and other coagulation parameters temporarily. In DSS and DHF the prophylactic platelet transfusion, the platelet count, prothrombin time ratio (PTR), PTT returned to pre transfusion level within 5 hours. This indicates lack of clinical marker for intervention which happens to target platelet count. This nurtures suspicion that platelet counts alone may not be a cause for bleeding diathesis in dengue fever.[19]

The incidence of hemorrhage was same in prophylactic platelet transfusions and no platelet transfusion group as shown Lum LC study[20] and in other studies there was any difference in bleeding incidents between transfused and non-transfused patients.[21] In spite of increasing platelet count due to platelet transfusion in half of the patients, it is neither prevented severe bleeding (WHO Grade 3) nor shortens the time to terminate the bleeding.[22]

So our objective of the study was to observe different modalities of treatment in dengue fever in our hospital and observe the overall response for 4-5 days with reference to rise in platelet count.

METHODS

Study design

It is a prospective observational study.

The study was carried out at the medical wards in JSS Medical college hospital, Mysore, Karnataka, India, a tertiary medical care centre from June 2010 to June 2011.

Ethical approval

Prior approval was obtained from ethical committee of the JSS Medical college Hospital, Mysore and informed consent was obtained by the study participants.

Inclusion criteria

At admission all suspected patients with dengue fever and above 18 years of age were assessed by the consultant (chief investigator). A detailed history was elicited and a thorough clinical examination was done. Data was collected in a prewritten proforma. Patients were screened with dengue NS1Ag, IgG ELISA, IgM ELISA, using DENGUE COMBO EZ DX AG AB Test, quantitative buffy coat for malaria parasite, serology for enteric fever, scrub typhus, leptospirosis; hemoglobin, total leukocyte count, differential leukocyte count, platelet count, hematocrit, peripheral blood smear, LFT, and a chest radiograph were done in all patients.

Exclusion criteria

Conditions which cause thrombocytopenia like HIV, autoimmune diseases, connective tissue disorder and vasculitis, ITP, malignancy were excluded by thorough clinical examination and relevant investigations whenever it was indicated. Diabetes mellitus, hypertension and patients with history of peptic ulcer

disease or hypersensitivity to corticosteroids and total leukocyte count more than 11,000/cumm was excluded from the study.

Sample size

For the purpose of the study dengue fever was suspected and screened and finally 128 patients were included into the study.

The daily measurement of platelet count was carried out in all patients from the day of enrolment to the fourth day of post treatment. Only serologically confirmed cases by dengue IgM ELISA were included, when their platelet count dropped below 100,000/cumm during the acute stage of the illness and were divided into three groups based on the platelet count at the time of admission.[24]

Group 1-mild risk: Those patients whose platelet count >40,000/cumm but < 100,000/cumm for the age and sex are observed and monitored carefully with supportive treatment without receiving platelet transfusion or steroids.

Group 2-moderate risk: Patients whose platelet count is in between 20-40,000/cumm belong to moderate risk category received only steroids i.e. inj Dexamethasone 4mg q8h for 4 days. If patient develops bleeding diathesis irrespective of platelet counts or fall in platelet levels less than 21000/cumm during the course of treatment were included into the high risk group and received both platelet and Inj. Dexamethasone 4mg IV q8h.

Group 3-severe risk: The patients belonging to this group had platelet count <20,000/cumm and they are at high risk of bleeding. Such patients received prophylactic platelet transfusion along with steroids i.e. Inj dexamethasone 4mg q8h for 3-4 days till the platelet levels reached above 100,000/cumm without bleeding diathesis.

The patients who were diagnosed with dengue fever were divided into three groups as mentioned above before observation and followed till they are discharged.

RESULTS

Continuous variables were expressed as mean±SD and categorical variables were expressed as number (%). Association between patient factors (age, sex, co-morbidities, gastrointestinal bleeding, haematocrit, platelet count, albumin, prothrombin time, renal failure, shock and dual infection) and mortality was studied using chi-square test or Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. P<0.05 was considered to be statistically significant

A total of 128 patients were admitted with features of DF during the study period; 109 (85%) were admitted during monsoon seasons. The mean age was 28.59±15 year; 15 (7.7%) were older than 60 year. Overall, the proportion of male and female were (2:1). Mean duration of fever was 4 days (range 2-6 days). The most frequent symptom was fever 128 (100%) followed by vomiting 52 (40.6%), headache (16.4%), diarrhoea and vomiting (14.68%), fatigue 54 (42%) and arthralgia 26 (20%), 28 (22%) had hepatomegaly and 6 (5%) had splenomegaly. The mean duration between onset of fever and sampling for initial investigation was 5 days (range 3-9 days). Thirty seven (28.9%) had leucopoenia defined as total count (TC) <4000 per/l; 23 (18%) had a platelet count of less than 20, 000 per/l and none had a platelet count of less than 10,000 per /l as mentioned in the Figure 1.

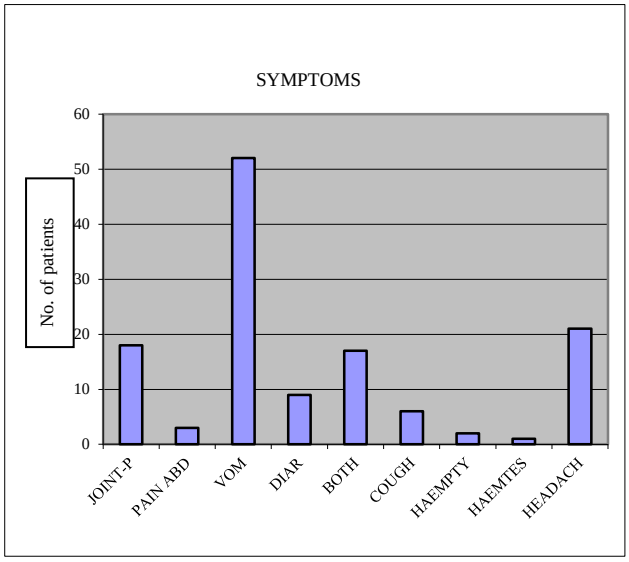

Figure 1: Different types of symptoms in dengue fever.

There were a total of 57 patients in group-1, 40 (70%) males and 17 (30%) females of these group the patient had predominantly having complaints of vomiting 15 (3.8%) followed by joint pains 12 (2.1%), headache 11 (1.9%), one patient had episode of hemoptysis, there were 3 diabetics and 2 hypertensive's . In this group there was no evidence of bleeding skin manifestations like petechiae or purpura,11 patients had leucopenia, 57 of them were IGM positive and 30 were IGG positive . NS1 antigen was positive in 16 patients and abnormal LFT was found in 10 patients, the lowest platelet count observed in this group was 4000, 4 patients had evidence of polyserositis, and 4 patients had dual infection along with dengue fever, where 3 patients had positivity for leptospirosis and one patient was positive for QBC MP.

There were 34 patients in group B, 25 males and 9 females, the most commonest symptom was vomiting 21, there was no evidence of bleeding in these patients one of them were hypertensive 10 patients had evidence of leucopoenia, 34 of them were IGM positive, 16 of them were IgG positive and 14 were NS1 positive. The lowest platelet count in this group was 1000 and 9 patients had

evidence of abnormal LFTs and one patient had evidence of polyserositis.

There were 37 patients in group C out of which 19 were males and 18 were females, the commonest symptom in this group is vomiting 16, 1 patient had hematemesis, there were 4 hypertensive's in this group, 13 patients had leucopenia 37 of them were IGM positive, 20 of them were IGG positive and 6 were NS1 positive. The lowest platelet count in this group was 2000 and 12 patients had evidence of abnormal LFTs and 3 patients had evidence of polyserositis.

DISCUSSION

Dengue infection causes significant morbidity and mortality throughout the world. The recommended treatment is only supportive care with careful fluid replacement, without specific treatment available at present.[5] The common objective in treating dengue patients with severe thrombocytopenia is to stabilize the platelet count which will avoid the major risk of bleeding.[23]

Corticosteroid has wide range of effects on immunological processes including their potent anti-inflammatory actions. Cochrane database of systematic reviews 2006 accomplished that there is not enough evidence to validate the use of corticosteroids in DHF and DSS and advised the need for large randomized controlled trials.[6]

In our study a gradual raise in platelet count was observed over four days in all the three groups which were in concordance with the natural history of recovery of platelet count in dengue infection. Surprisingly the increase of platelet count was seen in no intervention group. Similar observation of recovery of platelet count after a maximum drop with increasing platelet count gradually over three days without any intervention was observed in Sri Lankan study.[5]

The use of steroids without excluding the inter current infection in dengue fever may worsen the illness leading to increased morbidity and mortality due its immunosuppressant effect.[24,25-29]

Prophylactic platelet transfusion can be avoided without compromising patient wellbeing; in stable dengue fever patients without bleeding diathesis. Prophylactic platelet transfusion in dengue patients may be avoided till the platelet count reaches below 10 x 109/l in the absence of bleeding diathesis.

Increase of platelet counts through transfusion in the nonexistence of major bleeding has not given any protective benefits from bleeding in dengue fever. Timely recognition of dengue with rapid correction of hemodynamic parameters remains the important entity to avoid hemorrhagic complications which results in good clinical outcomes.

Platelet transfusion in spite of increasing platelet count in half of the patients neither prevented a severe bleeding (WHO grade 3) nor shortens the time to terminate the bleeding.[22] Platelet transfusion is associated with a risk of severe adverse reactions as shown in one study, where 2% of the platelet transfusions were linked with a severe unfavorable reaction.[22] In another study, deaths occurred due to platelet transfusion were 0.015% (20 of 1,712 transfusions).[30] However, there was no reported death attributable to platelet transfusion in our study. The possible pathogenesis of thrombocytopenia in dengue fever are enhanced peripheral destruction of antibody coated platelets, acute bone marrow suppression leading to a megakaryocytic condition and increased destruction of platelets by the reticuloendothelial system which helps to plan for the future research in severe complications of dengue fever.[2,3]

Our study demonstrated that the all three groups are similar in the increasing platelet count in dengue fever with thrombocytopenia patients (Figure 2). The rise in mean platelet count remained similar in all the groups. So the results of our study are in concordance with the conclusion opined by the Cochrane review.[7]

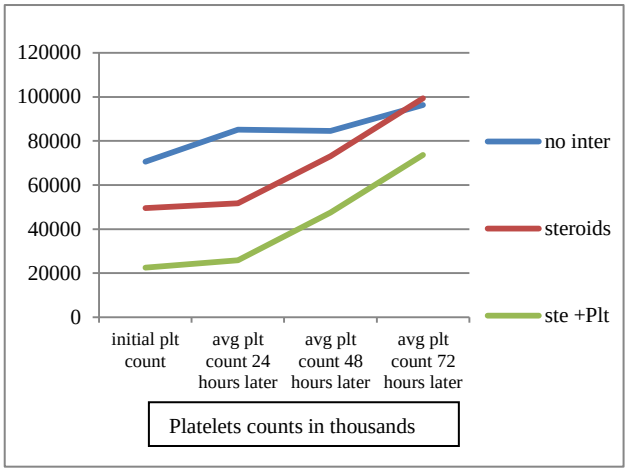

Figure 2: Comparison of effect of treatment on platelet count in three different groups.

However the lowest level of platelet count in dengue fever without bleeding is still controversial. This was supported in our study where bleeding was not seen in three patients with platelet count less than 5000/cumm.

Our study has several limitations. It is an observational study and lacks of randomization which might have resulted in treatment bias, there were less number of subjects in the study and number of cases and base line platelet count were different in all three groups.

CONCLUSION

This study infers that the need for formulation of new guidelines for platelet transfusion in dengue fever with thrombocytopenia. We also suggest a constant coordination between physician and transfusion specialists for the implementation of the same to give necessary treatment to save patients.

It is well known entity to give platelets in patients with dengue fever with thrombocytopenia worldwide however indications for the same and patient's condition may vary. Since there is high risk of transfusion reaction with platelet transfusion or blood components it is better to follow standard guidelines to treat patients in dengue fever. This helps treating physician to give better Treatment but also helps him to substantiate himself in explaining the unexpected bleeding diathesis during the course of illness.

Because our results revealed that there were no significant benefits of prophylactic platelet transfusion or steroids among adult patients with dengue fever. These results are similar to other studies involving different cohorts, so it is better to avoid steroids and prophylactic platelet transfusion given in acute uncomplicated dengue infection.[28-30] This approach will save precious blood products and will reduce unnecessary patient exposure to transfusion risks.

Therefore, dengue fever with thrombocytopenia without bleeding diathesis can be managed with supportive therapy as mentioned in WHO guidelines.

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