Effect of prednisolone during defervescence in dengue haemorrhagic fever: an open label controlled study

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ABSTRACT

Introduction: Immune-mediated destruction of platelets is thought to be one mechanism of thrombocytopenia seen after the viraemic phase of dengue haemorrhagic fever (DHF). Steroids are effective in the treatment of idiopathic thrombocytopenic purpura (ITP) which has a similar pathogenesis.

Objective: To evaluate the efficacy of prednisolone in the rate of resolution of thrombocytopenia and development of complications in patients recovering from DHF grade I and II

Method: An open label controlled study was carried out among 35 patients taking inward treatment at Teaching Hospital, Kandy between 31/08/2006 and 02/06/2007. Treatment group received prednisolone 10 mg tds with omeprazole 20 mg bd in addition to standard treatment. Control group received standard care only.

Results: There were 20 and 15 patients in treatment and control groups respectively. Control group had a mean rate of platelet rise significantly higher than that of treatment group. (58×10^9 /L /day vs. 27×10^9 /L /day; $p = 0.05$) No one developed predefined complications or adverse effects attributable to prednisolone.

Conclusion: This preliminary study has several limitations such as small sample size and laboratory data obtained from multiple sources. Therefore, large scale double blinded randomized controlled studies are needed before making recommendations on using steroids in patients with dengue haemorrhagic fever.

Introduction

Dengue infection is an important public health problem globally infecting about 50–100 million individuals every year living in the tropics and subtropics [1]. It is currently considered the most important communicable disease in Sri Lanka [2].

The bleeding diathesis in dengue is caused by vasculopathy, thrombocytopenia, platelet dysfunction and coagulopathy. Thrombocytopenia occurs due to bone-marrow suppression in early phase combined with increased peripheral destruction of platelets during the febrile and early convalescent phase of the disease [3]. Thrombocytopenia occurs in idiopathic thrombocytopenic purpura due to production of autoantibodies against platelet cell surface antigens for which steroids are considered the first line treatment which is thought to improve platelet counts by impairing the clearance of antibody coated platelets by tissue macrophages and through inhibition of antibody production [4]. Similar antibodies that cross-react and cause cell lysis are known to occur following dengue infection [5].

Steroids administered in dengue infection have shown both beneficial [6] and neutral effects [7,8]. In spite of these uncertainties steroids are still used in dengue infection by local clinicians [9].

This study was carried out to assess whether the use of steroids in defervescence period of dengue haemorrhagic fever (DHF) can,

a) increase platelet counts more rapidly and

b) minimize development of complications

thereby making it possible to discharge patients early minimizing hospital stay and thus cost to the government.

Methods

The study was carried out in two general medical units in Teaching Hospital, Kandy during 31/08/2006 and 02/06/2007. Participants were eligible if they belonged to DHF Grade I or II according to the WHO classification [10] with positive dengue antibodies. Patients should be fever free for ≥ 24 hours and should have a platelet count ≤ 50 × 109 /L to be included in the study. Patients were excluded if they had history of peptic ulcer disease or hypersensitivity to corticosteroids. Patients fulfilling above criteria admitted to one unit were given prednisolone 10 mg three times a day combined with omeprazole 20 mg twice a day for a maximum of three days in addition to standard treatment as outlined by the Ministry of Health guidelines on management of dengue [2]. Patients admitted to the other unit were recruited as the control group and received only the standard care. No formal randomization was carried out.

The outcomes measured were the rate of increase of platelets, rate of decrease in packed cell volume (PCV) and development of major complications. Major complications considered were development of WHO grade III or IV DHF, major bleeding requiring blood / platelet transfusions and myocarditis. Patients were also monitored for steroid related adverse effects.

The study was approved by the hospital ethics committee and informed verbal consent was taken from each subject.

The estimated sample size for each arm to detect a 10% treatment effect was 90 subjects. Data were analyzed using SPSS-13 software.

Results

The trial had to be abandoned prematurely as the dengue epidemic seen during the study period came to an end. 210 patients were assessed for eligibility and 35 patients, 20 in study group and 15 in control group, completed the trial. (Fig 1)

The age of the patients ranged from 14 - 60 years with a male to female ratio of 23 : 12. There were 11 and 24 patients in DHF grade I and grade II categories respectively. Baseline characteristics of age, gender and DHF grade did not differ significantly between the treatment and control groups.

IgM antibodies were positive in all subjects. IgG antibodies were negative in two patients and not done / reported in 2 patients. Tourniquet test was negative in 11 (45.8%) patients with symptoms or signs of spontaneous bleeding. (i.e. DHF Grade II).

Mean rate of platelet rise was 27.5×10^9 /L /day and 57.9×10^9 /L /day in treatment and control groups respectively. (P = 0.05) Mean rate of fall in PCV was 2.6 %/day and 2.4 % /day in treatment and control groups respectively. The scatter plots for both these outcomes demonstrated few outliers deviating from the trend of the majority. (Fig 2 and Fig 3)

Pre specified subgroup analyses were not carried out as the sample size was small.

None of the patients developed the pre specified complications during the study period.

None in the treatment group developed adverse effects that can be attributed to prednisolone.

Figure 1 - Recruitment of participants for the trial

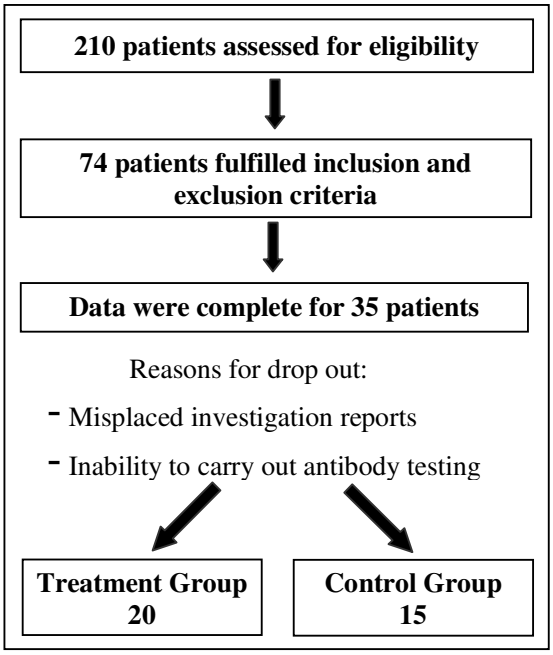


Figure 2 - Distribution of rate of platelet increase in treatment and control groups

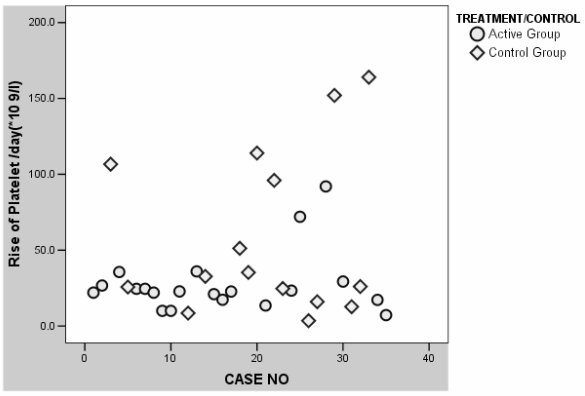
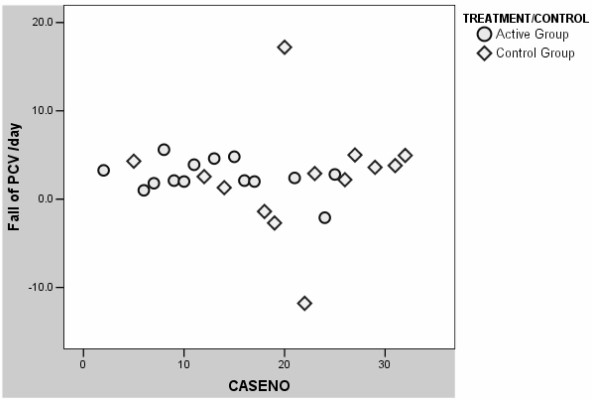


Figure 3 - Distribution of rate of PCV decrease in treatment and control groups



Discussion

The results of our study revealed a marginally significant difference in the mean rate of platelet increase between treatment and control groups showing that prednisolone adversely affects the recovery from DHF. Nonetheless, we speculate that this apparent difference most probably has arisen from the few outliers in the control group.

Due to practical constraints the blood samples were analyzed by different medical laboratory technicians leaving room for inter-observer variations. If sample size was reasonably large then this error could have been minimized. When data were reanalyzed removing the outliers there was no difference in rate of platelet rise between the two groups (Data not shown).

Further, absence of a similar trend in the rate of fall in mean PCV weakens the possibility of a true difference in mean rise of platelets between the two groups. During the recovery phase of dengue infection platelet count rises due to increased production of platelets in the hypercellular marrow [3]. If corticosteroids were to delay the rise in platelets marrow production should be affected. One remote possibility is that steroids might hinder the clearance of dengue virus from the bone marrow prolonging its marrow suppressive effect. Moreover, the dose and duration of prednisolone may have been inadequate to halt or retard the immune mediated thrombocytopenia. The recommended dosage regimen in adult idiopathic thrombocytopenic purpura exceeds the dosage and duration of treatment employed in this study [11].

Kularatne SAM and colleagues have shown in a randomized controlled study that a short course of dexamethazone in dengue fever during febrile thrombocytopenia does not show a significant benefit in increasing platelet count [8]. As the mechanism of thrombocytopenia in febrile phase is mainly direct bone marrow suppression by the virus, these results does not completely rule out a favourable effect of steroids during the defervescence.

We have observed that the tourniquet test has no relationship to the clinical features of haemorrhage in our patients. This has been observed by other workers calling for a reassessment of WHO categorization of DHF [12].

There were several limitations in our study. Sample size was smaller than that required to show a moderate difference. Laboratory tests were carried out in different laboratories by different technicians. Lastly the patients and the doctors were not blinded to treatment.

Evidence based recommendations on whether to administer steroids during defervescence phase of DHF is still lacking and cannot be drawn from the current study.

Larger double blind multi center randomized control trials are needed to answer this question.

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