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High Dose Corticosteroids – A Boon or Bane in Dengue Fever with Thrombocytopenia: A Case Control Study

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Abstract: ***Dengue infection is an important public health problem globally infecting about 50–100 million individuals every year. The increased peripheral destruction of the antibody coated platelets has been strongly suspected as the possible mechanism for thrombocytopenia in Dengue Fever. Corticosteroids are highly effective anti-inflammatory agents, frequently employed as adjunctive therapy in disease states where the host immune response is thought to contribute significantly to disease pathogenesis. This was a case control study about the effect of high dose corticosteroids on platelet count in dengue fever patients. The study was conducted on 80 patients with dengue NS1+ve with platelet count less than 1, 00,000 cu/mm. The study group received intravenous dexamethasone 16 mg initially, followed by 8 mg every 8 hours, thereafter for 4days. The control Group received only IV fluids and antipyretics whenever necessary. From this study we found that there was no significant difference in trends of increasing platelet counts between the two groups. The hospital stay was similar in both the groups, without any mortality and none of them developed shock or were admitted to intensive care during the study period of five days. In view of these observations, we conclude that the empirical use of steroids may be avoided in dengue fever with thrombocytopenia as high dose dexamethasone lacks efficacy in increasing the platelet count in thrombocytopenic dengue patients. The drawback of our study was, it was not a double blind placebo controlled trial and there were less number of subjects and cases of DHF and DSS were not included.***

Keywords: Dengue fever, Thrombocytopenia, Corticosteroids, platelet count

1. Introduction

Dengue infection is an important public health problem globally infecting about 50–100 million individuals every year (1). The Dengue infection is the most rapidly spreading mosquito-borne viral disease in the world. The case fatality rates for the south-east Asian region are 1%, but in India, Indonesia and Myanmar, focal outbreaks have reported rates of 3-5 %(1). A broad spectrum of disease manifestations is seen, ranging from asymptomatic infection to a systemic plasma leakage syndrome typically accompanied by thrombocytopenia and coagulation derangements. The increased peripheral destruction of the antibody coated platelets has been strongly suspected as the possible mechanism for thrombocytopenia in Dengue Fever. The other mechanism includes acute bone marrow suppression which leads to a megakaryocytic condition and enhanced platelet destruction by the reticulo-endothelial system

Thrombocytopenia which is commonly seen in patients with Dengue fever might sometimes lead to life threatening complications like Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) (4). Attempts have been made globally to combat these life threatening complications and find a better way to treat the dengue fever (5). Corticosteroids are highly effective anti-inflammatory agents, frequently employed as adjunctive therapy in disease states where the host immune response is thought to contribute significantly to disease pathogenesis. It has been well established that steroids are very effective in increasing the platelet count in immune thrombocytopenia (ITP), which is mediated by autoantibodies against platelet cell surface antigens(6). Here the corticosteroids act by impairing the clearance of antibody coated platelets by tissue macrophages and through inhibition of antibody production. As the mechanism involved in Thrombocytopenia in Dengue fever is similar, it would be justified to use steroids for thrombocytopenia in dengue infection.

However there are limited studies which have assessed the pros and cons of using corticosteroid therapy for thrombocytopenia in Dengue fever. The studies available show inconclusive evidence regarding the benefits of Corticosteroid therapy in increasing the platelet count in Dengue fever patients and have opined the need for larger meta-analysis to be done regarding the same for further reliable results. The objective of this study was to test the efficacy of intravenous high dose dexamethasone (Inj dexamethasone 8mg IV q8h for 5 days) on the mean platelet count in the acute stage of dengue fever with thrombocytopenia and to monitor the development of any complications, side effects from the corticosteroid therapy.

2. Materials and Methods

This study was carried out on the patients admitted in SSIMS & RC, tertiary medical care centre, from Oct 2016 to Oct 2017. At admission, all the suspected patients with dengue fever, who were above 18 years of age, were assessed. A detailed history was elicited and a thorough clinical examination was done. The data was collected in a prewritten proforma. A written informed consent was obtained from all the patients included in the study. The patients were told that they were free to withdraw from the

trial at any time if they wished. The patients were screened for Dengue NS1Ag, IgG ELISA, IgM ELISA, peripheral smear for malarial parasite, Widal test ,Haemoglobin, Total leukocyte count, Differential leukocyte count, Platelet count, Haematocrit, Peripheral Blood smear, coagulation profile and LFT, were done in all patients. The chest radiographs were taken whenever indicated. Only the serologically confirmed cases of dengue were included, when their platelet counts dropped below 100000/cumm during the acute stage of the illness. The conditions which cause thrombocytopaenia like HIV, Autoimmune Diseases, Connective Tissue disorders and Vasculitis, ITP, Malignancy were excluded by thorough clinical examination and relevant investigations whenever it was indicated. The patients with Diabetes mellitus, Hypertension, hypersensitivity to corticosteroids were excluded from the study.

The patients with an evidence of bleeding or shock were excluded, as they needed a close management and treatments such as platelet transfusions, which would have compounding effects on the study outcome. Informed consents were obtained from the study participants. The sample size was calculated according to the Formula N=Z2pq/d2 with a 4% prevalence. (Z-standard value, d - margin of error, p is proportion of prevalence, q = 1-p).

For the purpose of the study, dengue fever was suspected and screened in 185 patients. After the exclusion of 105 patients, the remaining 80 patients who were positive for dengue serology and had thrombocytopenia were included in the study. They were allotted randomly, 40 into the study group and 40 into the control group, by blocked randomization by using a fixed blocking method, into the open labelled study. The study group received intravenous dexamethasone 16mg initially, followed by 8 mg every 8 hours, thereafter for 4 days and IV fluids were given whenever they were required. The control Group received only IV fluids and antipyretics whenever necessary. Daily monitoring of the platelet count, temperature, pulse, BP, haematocrit value, blood glucose and electrolytes, coagulation profile was done for four days of the study period.

The mean rise in the platelet count was measured daily in both the groups, which was taken as the primary outcome. The statistical analysis was carried out by SPSS, version 24 and then the baseline variables (Hb%, age, sex, haematocrit) were compared between the study and the control groups using the student's t test to ensure a correct and a comparable allocation. The differences in the continuous data (mean platelet count) were compared by using the independent sample "t" test. The trends of change in the platelet counts between the study and the control groups according to the days were calculated by using the repeated measure (ANOVA) test.

3. Results

The demographic and the haematological features of both the groups were comparable, as shown in [Table/Fig-1]. There were no significant differences in the base line characters like the mean (SD) age, sex, the mean duration of the illness during the enrolment, Hb%, haematocrit, and the platelets in the both groups at the time of the enrolment. There were 13(43%) males and 17(56%) females in the study group and 14(46%) males and 16(53%) females in the control group. The mean (SD) age in the study group was 32.2(10.8) years and in the control group was 33.2(10.2). The daily assessment of clinical features such as nausea, vomiting, body temperature, pulse rate and blood pressure (mm Hg) between the two groups showed no significance (p> 0.05). Secondary outcomes such as the mean difference of haematocrit, Hb, WBC showed no significant difference between the two groups during the 4 days.

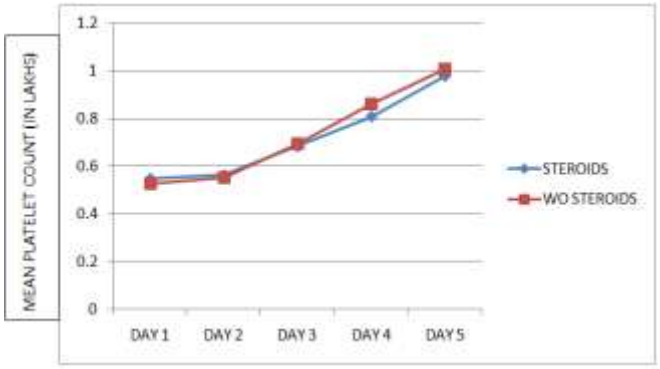
On day 1, at baseline, there was no significant difference in mean platelet counts between the study and control groups. This phenomenon continued during the study period of 5 days (table 3). In both groups the mean platelet counts increased, the rise in the mean platelet value being more in the control group than the study group, however it was not significant (fig 2). The ANOVA statistics indicated significantly increasing trends of mean platelet counts in both the study andcontrol groups (table 4). However, there was no significant difference in trends of increasing platelet counts between the two groups. The hospital stay was similar in both the groups, without any mortality and none of them developed shock or required Transfusions or admitted to intensive care during the study period of five days.

	Characteristics	Study group no & SD	Control group no & SD	p value
Gender	Male	13 (43.3)	14 (46.6)	-
	Female	17 (56.6)	16 (53.3)	-
Age	Mean age (SD) years	32.2 (10.8)	33.2 (10.2)	0.774
Illness	Mean (SD) days of illness at enrollment	4.1 (1.9)	4.6(2.1)	0.693
Haemoglobin	Mean (SD) hb g/dl	14.06 (2.2)	13.19 (1.69)	0.816
Heamtocrit	Mean & SD	40.1 (6.3)	40.1 (5.26)	0.376
	Total in group	40	40	

[Table/Fig-1]: Demographic and haematological features of the sample selected for study and control group

Days	Group	Mean platelet count (in Lakhs)	Standard deviation (in Lakhs)	t value	p value
Day 1	Control	0.547	0.28	0.7619	0.529
	Study	0.529	0.2401		
Day 2	Control	0.563	0.234	0.886	0.813
	Study	0.556	0.202		
Day 3	Control	0.683	0.287	0.794	0.187
	Study	0.696	0.167		
Day 4	Control	0.808	0.323	0.3506	0.252
	Study	0.862	0.152		
Day 5	Control	0.978	0.38	0.556	0.137
	Study	1.01	0.173		

[Table/Fig-2]: Mean platelet counts of control and study group over days and results of independent sample "t" test



[Table/Fig-3]: Estimated marginal means of mean platelet count in study and control group

4. Discussion

The Dengue infection causes significant morbidity and mortality all around the world. The current recommended treatment is largely supportive, with fluid replacement and with no specific treatment available at present (4). The common goal in treating these patients with severe thrombocytopenia is to stabilize the platelet count, which will prevent the major risk of bleeding (7). Corticosteroids are potent anti-inflammatory agents that have a wide range of effects on the immunological processes. Although not mentioned in the WHO guidelines on the management of dengue, corticosteroids are used empirically, based on the presumed immunological basis of complications of dengue, particularly in the South East Asian countries. They are thought to be effective for stabilizing the capillary permeability and have been used in addition to other supportive therapy. (4)

The evidence for the benefit or a lack of benefit of corticosteroids in thrombocytopenia and bleeding, as well as the other complications of dengue, is not clear. The Cochrane Database of Systematic Reviews, 2006, concluded that there was insufficient evidence to justify the use of corticosteroids in DHF and DSS and it concluded the need for large randomized controlled trials.(7) Kularatne SAM, et al in a descriptive study of a series of dengue patients, observed that, after a maximum drop in platelet count, it increased gradually over the next 3 days without any intervention(9). Therefore, mere thrombocytopenia without any bleeding tendency in dengue infection could be left untreated under close monitoring pending natural recovery(9). Futrakul et al., in a prospective study showed a positive response with a high dose of methyl prednisolone and mannitol in severe DSS which was unresponsive to fluid replacement (10). Hydrocortisone has been used with variable results in DSS (11, 12). In a case report of dengue fever, long lasting myositis resolved with steroid treatment (13). Another study showed an absence of cortisol insufficiency in a series of 62 children with dengue infection, including DHS and DSS, by measuring serum cortisol values, further supporting the clinical evidence of lack of efficacy of corticosteroids in patients with dengue infection. Panpanich R et al., observed an increased mortality after the use of steroids in DSS and DHF and opined that it was difficult to conduct a study on life threatening illnesses like DSS and DHF, as steroids would have compounding effects on the outcome of the disease (8). Therefore in our study we included only the patients with dengue fever with thrombocytopenia, without bleeding diathesis or dengue shock syndrome.

Sam Kularathne et al., used low dose dexamethasone ie 4mg initially, followed by 2mg q 8 hours for 4 days in dengue fever with thrombocytopenia (platelets less than 50000/cumm) in a placebo controlled study and concluded that it was not effective in increasing the platelet count. They advised to conduct similar studies using high dose dexamethasone (11). Similarly KC Shashidara et al; also conducted a similar study with high dose of dexamethasone i.e. 8mg initially, followed by 4mg IV q8hrs for 4 days, but there was no difference in the rise in the mean platelet counts in both the groups which was the same result seen from our study. In our study, a gradual rise in the platelet count was observed over five days in both the groups, which was in concordance with the natural history of the recovery of the platelet count in the dengue infection.

There were no drop outs and all the patients improved without worsening of the clinical condition or mortality in both study and control group. This ruled out the possible risk of worsening of the illness due to the high dose short course steroids in our study, because of exclusion of the patients with dengue fever with an secondary infection. Several studies have shown that the empirical use of steroids in sepsis is still controversial (17-20). The use of steroids, in patients with secondary infection along with dengue fever, may worsen the illness, leading to increased morbidity and mortality due to its immunosuppressive effect (21-23).

5. Conclusion and Future Scope

In view of these observations, the empirical use of steroids may be avoided in dengue fever with thrombocytopenia. Our study demonstrated that high dose dexamethasone lacks efficacy in increasing the platelet count in thrombocytopenic dengue patients. The rise in the mean platelet count (the primary outcome) remained similar in both the control and the study groups. However, the lowest level of platelet count in dengue fever without bleeding is still controversial. The drawback of our study was, it was not a double blind placebo controlled trial and there were less number of subjects and cases of DHF and DSS were not included.

Therefore, dengue fever with thrombocytopenia without complications like DHF and DSS can be managed with supportive therapy, as has been practised routinely. Finally we conclude that, a short course of high dose dexamethasone therapy is ineffective in increasing the platelet count in patients with Dengue fever.

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