To determine the correlation of severity of thrombocytopenia, with vitamin B12 deficiency in patients of dengue fever

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***Abstract*---**Objective: To determine the correlation between the severity of thrombocytopenia, hospital stay, hematological, & biochemical parameter with vitamin B12 deficiency, &role of vitamin B12 supplementation in patients of dengue fever. Methodology: 100 dengue patient were included in the study. All baseline parameter were examined along with platelet count and vitamin B12 level. Results: platelets count and vitamin B12 were low in dengue patient and platelet count is positively correlated with vitamin b 12 level.(r=0.57, p value < 0.05). Conclusion: a significant positive correlation between the severity of thrombocytopenia &vitamin B12 deficiency was observed. Vitamin B12 supplementation improved the hematological and biochemical parameters also having a significant

association with platelet recovery in the form of less requirement of random donor platelets transfusion.

Introduction

Dengue is a mosquito-borne viral disease that has rapidly spread to all regions of the world health organization in recent years. Dengue virus is transmitted by female mosquitoes mainly of the species *Aedes aegypti* and, to a lesser extent, *Ae. Albopictus* [1].Dengue is caused by a virus of the Flaviviridae family and there are four distinct, but closely related, serotypes of the virus that cause dengue (DENV-1, DENV-2, DENV-3, and DENV-4). Recovery from infection is believed to provide lifelong immunity against that serotype.

The incidence of dengue has grown dramatically around the world in recent decades. A vast majority of cases are asymptomatic or mild and self-managed, and hence the actual numbers of dengue cases are under-reported. Many cases are also misdiagnosed as other febrile illnesses [1]. A study on the prevalence of dengue estimates that 3.9 billion people are at risk of infection with dengue viruses. Despite a risk of infection existing in 129 countries [3], 70% of the actual burden is in Asia [2]. After feeding on a DENV-infected person, the virus replicates in the mosquito midgut, before it disseminates to secondary tissues, including the salivary glands. The time it takes from ingesting the virus to actual transmission to a new host is termed the extrinsic incubation period. The extrinsic incubation period takes about 8-12 days when the ambient temperature is between 25-28°C [4-6].

The disease spectrum of symptomatic dengue virus infections was grouped into three categories: undifferentiated fever, dengue fever (DF), and dengue hemorrhagic fever (DHF). DHF was further classified into four severity grades, with grades III and IV being defined as dengue shock syndrome (DSS) [7]. The mechanisms involved in thrombocytopenia and bleeding during DENV infection are not fully understood. Several hypotheses have been suggested to elucidate the mechanism involved. In this context, DENV could directly or indirectly affect bone marrow progenitor cells by inhibiting their function [8] to reduce the proliferative capacity of hematopoietic cells[9].

Indeed, there is evidence that DENV can induce bone marrow hypoplasia during the acute phase of the disease [10]. Besides platelets counts, the functional disruption of these cells is associated with significant deregulation of the plasma kinin system and the immunopathogenesis of dengue [11]. In addition, DENV infection induces platelet consumption due to disseminated intravascular coagulation (DIC), platelet destruction due to increased apoptosis, lysis by the complement system, and the involvement of antiplatelet antibodies [12–14]. Here, we discuss the relevance of platelets in physiology and their implication in dengue pathogenesis, acting both as avictim of infection and aneffector cell of the antiviral immune response. Objective of the study was to determine the correlation between the severity of thrombocytopenia, hospital stay,

hematological, & biochemical parameter with vitamin B12 deficiency, &role of vitamin B12 supplementation in patients of dengue fever.

Methods

Study Design and period

A prospective observational study was done, in the inpatient department Uttar Pradesh University of Medical Sciences Saifai Etawah Uttar Pradesh, during the period from July 2020 to December 2021

Study Setting

Sample size of 100 patients with dengue fever either positive for NS1 antigen or IgM ELISA with prolonged thrombocytopenia admitted to inpatient department were included in the study with informed consent.

Data Collection

Data collected from case record of the patient during hospital inpatient admission with informed consent from the patient attendant, detailed information with date of admission, clinical, sociodemographic variable, laboratory investigation, number of random donor plasma transfused, duration of hospital stay collected from case sheet.

Participants

Patient willing to give consent and participate in the study.The patientis either not willing to give consentor with underlying malignancy, hematological disorders, sepsis, Chronic Liver Disease.Patients using drugscausing thrombocytopenia & other causes of fever with thrombocytopenia other than dengue fever were excluded from the study.Patients attendinginpatient Department of Medicine UPUMS Saifai were taken with informed consent from all the cases before their inclusion into the study.

We conducted a prospective observational study in the Department ofMedicine at Uttar Pradesh University of Medical Sciences, Saifai Etawah, admitted patients who were positive for NS1 antigen/IgM/ ELISA for dengue along with platelets counts less than 50000/µl and were showing slow recovery of platelets i.e., persisting below 50000/µl for 2 days or more, were included in the study. Patients with underlying malignancy, hematological disorder, chronic liver disease, septicemia, or use of any drug which may cause thrombocytopenia, were excluded from the study. Clinical features, hematological and biochemical parameters were noted and vitamin B12 levels were measured by ARCHITECT. Rapid donor platelet (RDP) transfusion was done if the patient was actively bleeding irrespective of platelet count or if platelet levels were less than 10000/µl.
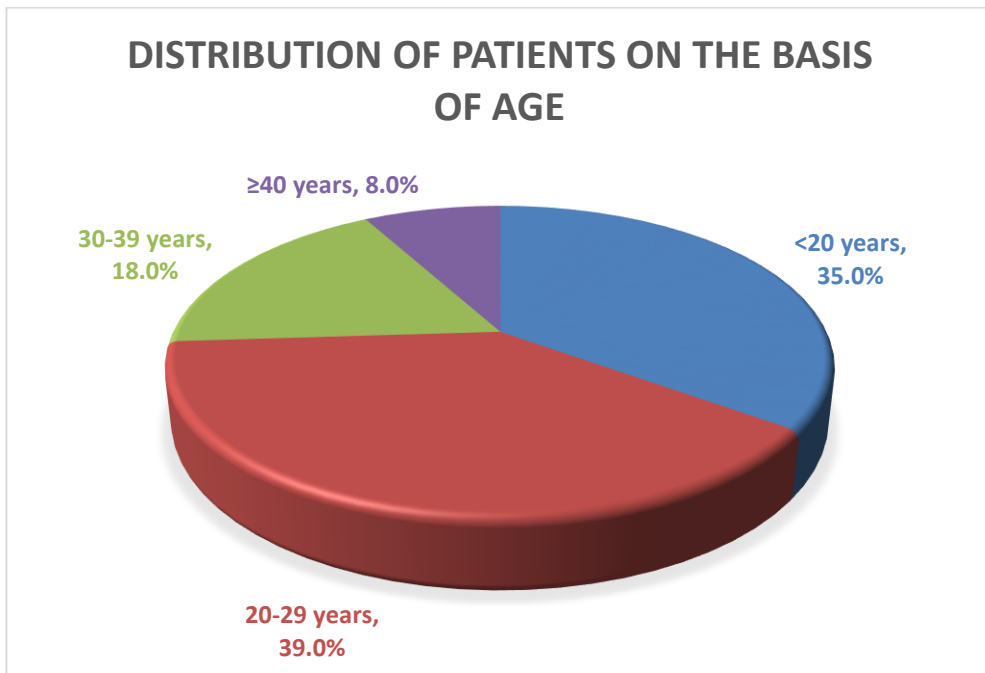
Statistical Analysis

All the data was noted down in a pre-designed study proforma. Data were analyzed using Statistical Package for Social Sciences, version 25 (SPSS Inc., Chicago, IL). Results for continuous variables are shown as mean ± standard deviation (SD), whereas results for categorical variables are shown as number (percentage). Analysis of Quantitative data between the two groups was done using paired t-test. A p-value < 0.05 was taken as a level of significance. Results were graphically represented where deemed necessary.
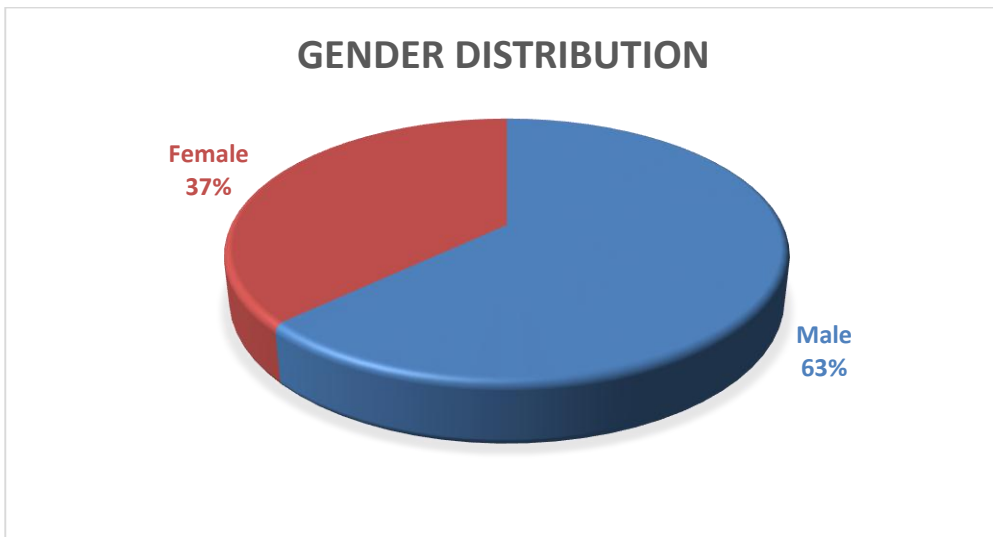
Ethical Consideration

Ethical clearance from Ethical Committee Uttar Pradesh University of Medical Sciences Saifai grantedwith reference number:1678/UPUMS/Dean(M)/Ethical/2020-21, Ethical clearance no 98/2019-20.

Results

During the 1.5-year study period from July 2020 to December 2021, a total of 100 dengue fever patients were included in the study. Out of 100 patients, 63 (63%) were males and 37 (37%) were females, mean age was (25.6 ± 8.78) years. For the study, purpose thrombocytopenia is classified into mild, moderate & severe thrombocytopenia. Vitamin B12 deficiency divided into two groups 1) deficient <190 pg/mL, 2) normal >190 pg/L. Patients with disease conditions causing thrombocytopenia like chronic liver disease, hypersplenism, hematological disorders, malignancy, sepsis, using drugs causing thrombocytopenia were excluded from the study. Out of within vitamin B12 deficient patients two groups were formed one whom vitamin B12 supplemented and another without vitamin B 12 supplementation. Hematological, biochemical parameters, need of rapid donor plasma transfusion & hospital stay compared between these Two study groups by standard statistical methods. Vitamin B12 deficiency divided into four groups B12 deficiency 1)<100 pg/L, 2)≥100-200pg/L 3)≥200-300pg/L 4)≥300pg/L. Total 52% of patients were vitamin B12 deficient, mean hospital stay among B12 deficient patients was (7.21 ± 3.1) days, compared to normal vitamin B12 was (4.67 ± 2.50) days. RDP requirement was high amongst B12 deficient (7.11 ± 1.90) compared to normal vitamin B12 level (3.79 ± 1.58) units. After vitamin B12 supplementation hematological and biochemical parameters improved significantly. There was a significant association between severity of thrombocytopenia, & vitamin B12 deficiency, vitamin B12 deficiency with the duration of hospital stay, recovery from illness, hematological & biochemical parameters.

DISTRIBUTION OF PATIENTS ON THE BASIS OF AGE

≥40 years, 8.0%

30-39 years, 18.0%

<20 years, 35.0%

20-29 years, 39.0%

- Out of 100 patients, 63 were male & 37 were female.

GENDER DISTRIBUTION

Female 37%

Male 63%

- Out of 52patients having Vitamin B12 deficiency, 38 (61%) were strictly vegetarian. 39% mixed

VITAMIN B12 DEFICIENCY   (N= 52)
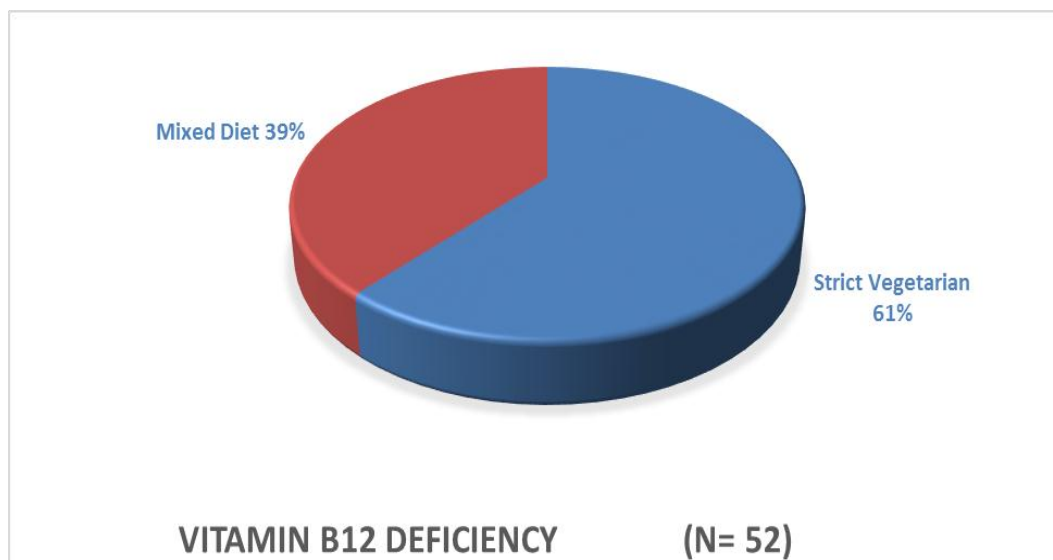
- Out of 100 patients, 52 patients were vitamin B12 deficient.

Level of Vitamin B12	No. of patients	Percentage
Vitamin B12 deficiency (<190pg/ml)	52	52.0
Normal Vitamin B12 (≥190pg/ml)	48	48.0

- Out of 52 patients 46 have severe thrombocytopenia & vitamin B12 deficiency.

Thrombocytopenia	Vitamin B12 deficiency Severity (<190pg/ml) (n=52)	Normal Vitamin B12 (190pg/ml to 950pg/ml) (n=48)	p-value
Mild	1 (1.9%)	11 (22.9%)	
Moderate	5 (9.6%)	9 (18.8%)	<0.001
Severe	46 (88.5%)	28 (58.3%)	

| Vitamin B12 Level	Number of patients
<100 Pg/L	16
100-200 Pg/L	42
200-300 Pg/L	26
>300 Pg/L	19

Out of 46 vitamin B12 deficient patients 24 patients, vitamin B12 supplementation was given. comparison group, who were not given B12 supplementation (n=28) was formed, statistical analysis was done to compare the number of units of random donor plasma required for transfusion to correct thrombocytopenia. In the vitamin B12, deficient group average requirement of random donor platelet was (3.79 ± 1.58) units who were supplemented with at least 5 days of injectable vitamin B12 along with random donor plasma, in whom

without B12 supplementation average requirement was (7.11 ± 1.90) unitswith vitamin B12 supplementation was (3.79 ±1.58) units. The number of days of hospital stay without & with vitamin B12 supplementation was (7.8 ± 2.25) & (7.04 ±1.78) days respectively.

	Without B12 Supplementation (n=28)	With B12 Supplementation(n=24)	P- Value
Number Of random donor platelet required	7.11 ±1.90	3.79 ±1.58	<0.001
Number of Days of Hospital Stay	7.8± 2.25	7.04 ±1.78	0.18

- There was a positive correlation between the severity of thrombocytopenia & vitamin B12 deficiency with a correlation coefficient of 0.5748.
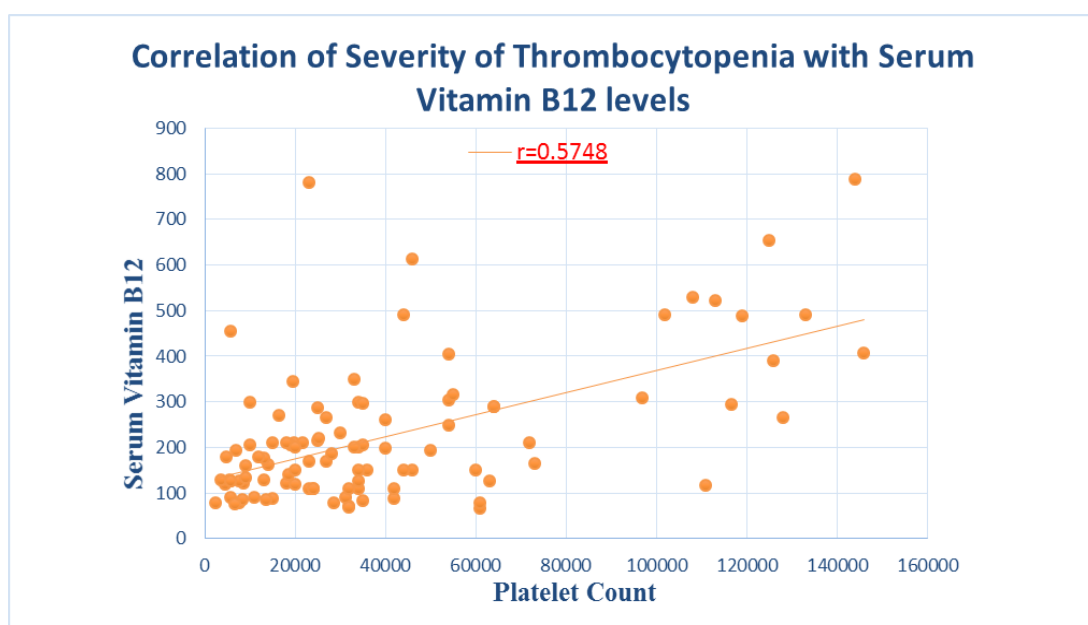
Hematological & Biochemical Parameters	BEFORE B12 SUPPLEMENTATION (n =24)	AFTER B12 SUPPLEMENTATION (n= 24)	P -Value
MEAN PLATELET VOLUME(fl)	13.57 ± 1.14	11.66 ± 1.16	<0.001
Mean Corpuscular Volume (fl)	110.75 ± 8.93	103.54± 9.16	<0.001
Hemoglobin	9.47 ± 2.80	9.65± 2.40	0.812
SGOT	115.79 ± 105.93	42.58 ± 17.71	0.003
SGPT	69.58 ± 44.65	37.83 ± 9.78	0.002
SERUM LDH	796.79 ± 486.46	475.33 ± 240.46	0.006

SERUM UREA	50.87 ± 28.59	40.58 ± 14.56	0.125
SERUM CREATININE	1.01 ± 0.51	1.01 ± 0.34	0.975

Discussion

Vitamin B12 acts as a co-factor during the synthesis phase of the cells in the bone marrow. So, Vitamin B12 deficiency causes thrombocytopenia. Serum Vitamin B12 levels are not frequently tested in patients being treated for thrombocytopenia secondary to the spectrum of dengue viral infection.**Error! Bookmark not defined.** Severe vitamin B12 deficiency may be associated with thrombocytopenia apart from anemia and leukopenia. Vitamin B12 deficiency is common Indian population; therefore, we planned this pilot study to test the hypothesis that vitamin B12 level may have a correlation with prolonged and severe thrombocytopenia in dengue patients.

In the present study, the majority of the mean age of subjects was 25.06±8.78 years. The majority39 (39.0%) patients belong to 20-29 years of age followed by 35 (35.0%) with Age<20 years, 18 (18.0%) patients with 30-39 years of age, and least 8 (8.0%) patients were from more than 40 years of age and 63 (63.0%) were male and 37 (37.0%) were female. Our findings were comparable to the study performed by Tak S et al**Error! Bookmark not defined.** in their study on severe thrombocytopenia in dengue fever and vitamin B12 level reported that a total of 40 subjects were included in their study. 21/40 were male and reaming were the female subjects (19/40). The mean age of patients was 25.0±12.0 years. Ramalingaiah MT et al**Error! Bookmark not defined.** reported that the majority of subjects were in the age group 31 to 40 years (26.0%), 50% were males and females respectively.

In our study, the majority 78.0% of the studied patients were suffering from IgM positive dengue and most of them were having fever (100.0%) followed by black 41.0%, Fever with Myalgia (12.0%). In a study done by Ramalingaiah MT et al15 out of 50 patients, 78.0% patients had dengue NS1 antigen-positive and 22.0% patients had dengue IgM positive. The most common clinical feature was fever followed by bleeding manifestations. A study done by Neeraja M et al21showed fever was the most common presenting complaint.The most common bleeding manifestation was bleeding gums. Ramalingaiah MT et al15reported, 48.0% of patients had bleeding manifestations which were 44.0% in our study. Bleeding manifestations were noted in 21.0% of patients in the study conducted by Laul A et al21. Astudy conducted by Senthamarai A et al22 showed similar results.

The majority 74 (74.0%) of patients have had severe thrombocytopenia followed by 14 (14.0%) moderate thrombocytopenia and 12 (12.0%) patientswho had mild thrombocytopenia and there were 52 (52.0%) of patients were found as vitamin B12 deficient and remaining 48 (48.0%) were had normal range of vitamin B12. In the present study, the vitamin B12 deficiency was in 52.0% of patients whereas 48.0% had normal vitamin B12 levels. The association between vitamin B12 and the severity of thrombocytopenia was statistically significant because the patients with deficiency of vitamin B12 were having significantly higher severity of thrombocytopenia (p<0.05). Our findings were byRamalingaiah MT et al15 who

reported thatamong subjects with no thrombocytopenia and mild thrombocytopenia, 100% had normal Vitamin B12 levels. Among those with Moderate thrombocytopenia, 62.5% had Vitamin B12 Deficiency and 37.5% had normal Vitamin B12 levels and among those with severe thrombocytopenia, 94.4% had Vitamin B12 deficiency and 5.6% had normal Vitamin B12 levels. There was a significant association between platelet count and Vitamin B12 levels. I n a study performed by Tak S et al**Error! Bookmark not defined.** for SDP was highest (3.0± 1.41) in a group with vitamin B12 level less than 100pg/L compared to group B12>300 pg/L (1.36±1.2860), although it was not statistically significant. This suggests that severe B12 deficiency may prolong the severity of thrombocytopenia, as in the current study SDP was transfused only if platelets persisted below 10000/µl.

In our study, the mean platelet count was significantly higher in the dengue patients with normal vitamin B12 levels as compared to the patients with vitamin B12 deficiency (p<0.05). Also the duration of hospital stay was significantly higher for Vitamin B12 deficiency (<190pg/ml) (7.21 ± 3.1 days) than Normal Vitamin B12 (190pg/ml to 950pg/ml) patients (4.67 ± 2.50 days) (p<0.05).

In a study conducted by Ramalingaiah MT et al15among the dengue patients with normal platelet count and mild thrombocytopenia, had normal Vitamin B12 levels. Among those with moderate thrombocytopenia, 62.5% of patients had Vitamin B12 deficiency, 37.5% patients had normal Vitamin B12 levels and among those with severe thrombocytopenia, 94.4% had Vitamin B12 deficiency and 5.6% had normal Vitamin B12 levels. Mean Vitamin B12 was significantly lower among those with severe thrombocytopenia. Similarly, there was a significant difference in mean Platelet transfusion and duration of hospital stay concerning Severity of Platelet count. In patientswith a decrease in B12 levels, there was an increase in need of platelet transfusion and increased duration of hospital and vice versa.

Tak S et al**Error! Bookmark not defined.**reported that platelet recovery time (time taken to recover to >20000/µl).[17] This parameter was selected during in-patient management as the platelets recover beyond 20000/µl and if the patient is otherwise fit, she/he is considered for discharge. Platelet recovery time was also maximum in B12300 pg/L (3.0±0days) and it was statistically significant. As it is clear from Table 2 more severe, the B12 deficiency was more prolonged was platelets recovery time.A similar trend was seen in the duration of hospital stay: Hospital stay (in days) was also highest in vitamin B12300 pg/L (3.64±0.5days) and it was statistically significant. As it is obvious from Table 3 as the severity of vitamin B12 deficiency increased so does the hospital stay. No published studies are measuring these parameters against vitamin B12 level so we cannot compare them with any other study.

A study by HottzED et al confirmed that platelets from DENV-infected patients exhibited classic signs of the intrinsic pathway of apoptosis, which include increased surface PS exposure, mitochondrial depolarization, and caspase-9 and caspase-3 activation. Moreover, all of these changes were observed when platelets from healthy subjects were directly exposed to DENV *in vitro*, which may contribute to thrombocytopenia development in dengue patients.[16] More recently, a prospective observational study by Noisakran S et al22using blood samples

from dengue-confirmed patients, as well as rhesus monkeys (RM) experimentally infected with DENV, revealed that DENV antigen was present in small vesicles of varying size and more frequently in anucleated cells associated with platelets. DENV RNA was observed in a highly enriched CD61(+) cell population from infected RM during the acute stage. These results suggest that virus-containing CD61(+) cells are directly linked to platelet dysfunction and low platelet count characteristics of dengue patients.

There are no large epidemiological studies to assess B12 levels in the Indian population but few studies suggest that Vitamin B12 deficiency is common in Indian populations with a prevalence range of 35.0% to 60.0%.[18,19] Vitamin B12 is an important factor required for erythropoiesis and thrombopoiesis. Approximately 10.0% of patients with symptomatic B12 (cobalamin deficiency) have significant thrombocytopenia.**Error! Bookmark not defined.** There are case reports associatingB12 deficiency with thromboticthrombocytopenic purpura (TTP) like the picture.[20]

The time of measurement in platelet level is not constant in all patients because it was measured at different times of illness in various patients. Hence, we cannot conclude at which stage of disease platelets started to decline. Study population includes age group of only 15-50 years beyond this range of age the pattern of correlation between thrombocytopenia and dengue could not be concluded Some patients may have low platelets levels due to other causes but this proportion is very minimal. So we did not evaluate for other causes of thrombocytopenia.

Vitamin B12 supplementation was given for a very short period so can't be decided whether the effect was due to vitamin B12 or confounding factors. A larger study is required to confirm our preliminary findings. The best approach would be to measure vitamin B12 level in a large cohort of dengue patients and plot it against platelets level. Another logical step should be to see the response to injectable B12 supplementation in such patients.

Conclusion

A total of 100 cases were studied,the majority of 78 (78.0%) patients were IgM positive and 22 (22.0%) patients were NS 1 positive on the basis of dengue profile. The mean age of subjects was 25.06 ± 8.78 years,majority 39 (39.0%) patients belong to 20-29 years of age followed by 35 (35.0%) with Age<20 years, 18 (18.0%) patients with 30-39 years of age and least 8 (8.0%) patients were from more than 40 years of age.

Fever was the major clinical feature (100.0%) followed by 41 (41.0%) black stool, 12 (12%) reported fever, myalgia, arthralgia 7 (7.0%) Epistaxis and4 (4%) patients reported fever and cough. Association between Vitamin B12 levels and severity of thrombocytopenia was statistically highly significant (p<0.01). Mean Platelet count and duration of Hospital stay concerning Vitamin B12 levels was also found to be significant (p<0.05) and duration of stay was much higher in vitamin B12 deficiencies patients and they also had a significantly lower level of platelet count. Vitamin B12 supplementation may improve the clinical outcome in the form of platelet recovery, duration of hospital stays, hematological& biochemical

parameters of dengue fever patients having severe thrombocytopenia, and vitamin B12 deficiency.

Vitamin B12 deficiency may be a contributing factor to the development of severe thrombocytopenia in dengue fever, particularly in the Indian population. Dengue fever patients with Vitamin B12 deficiency had moderate to severe thrombocytopenia and more bleeding manifestations. Those patients required more platelet transfusion and increased duration of hospital stay.

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