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EFFECT OF VITAMIN E & VITAMIN C SUPPLEMENTATION ON THROMBOCYTOPENIA IN DENGUE FEVER – A RANDOMISED CONTROLLED TRIAL IN CHILDREN AGED 2–12 YEARS

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Abstract

Background: Thrombocytopenia is a hallmark of dengue fever and significantly contributes to disease severity and bleeding complications in paediatric patients. Oxidative stress plays a key role in dengue pathogenesis, suggesting that antioxidant therapy may enhance haematological recovery.

Objectives: To evaluate the efficacy of Vitamin C and E supplementation on platelet recovery, bleeding incidence, and recovery time in children with dengue fever.

Methods: This double-blind, randomized, placebo-controlled trial was conducted at Dept. of Paediatrics, Saveetha Medical College and Hospital in Tamil Nadu, India. Sixty children aged 2–12 years with serologically confirmed dengue and platelet counts <100,000/mm³ were randomized equally into an intervention group (Vitamin C 500 mg/day + Vitamin E 200 mg/day for 5 days) and a control group (placebo). Primary outcome was mean platelet count on Day 5. Secondary outcomes included bleeding incidence, time to platelet recovery, and adverse events.

Results: All participants completed the study. The intervention group showed significantly higher mean platelet counts on Day 5 (~115,000/mm³ vs. ~80,000/mm³; $p<0.05$) and a greater rise from baseline (~52,500/mm³ vs. ~30,000/mm³). Bleeding incidence was reduced in the intervention group (6–10% vs. 20%), and time to platelet recovery was shorter (mean 4 vs. 6 days). No serious adverse events were reported.

Conclusion: Supplementation with Vitamin C and E significantly improves platelet recovery, reduces bleeding risk, and shortens recovery time in paediatric dengue patients. This antioxidant therapy is safe, cost-effective, and potentially valuable as an adjunct to standard dengue management, especially in resource-limited settings.

Keywords: Dengue fever, Thrombocytopenia, Paediatric, Vitamin C, Vitamin E, Antioxidants, Randomized controlled trial

INTRODUCTION

Dengue fever is a mosquito-borne viral illness that poses a significant public health burden, especially in tropical and subtropical regions such as Southeast Asia and India. An estimated 390 million infections occur globally each year, with approximately 96 million symptomatic cases, and children represent a disproportionately high percentage of hospitalizations and severe presentations(1). One of the hallmark hematological manifestations of dengue is thrombocytopenia, which closely correlates

with disease severity, heightened bleeding risk, and often necessitates inpatient care and close monitoring(2).

The pathogenesis of thrombocytopenia in dengue is multifactorial, involving mechanisms such as bone marrow suppression, immune-mediated platelet destruction, and increased peripheral sequestration(3). These complex pathways contribute to the rapid decline in platelet count observed in many dengue patients and underscore the need for interventions targeting both viral and host responses.

In addition to these classical pathways, oxidative stress has emerged as a pivotal contributing factor. Elevated levels of oxidative stress markers—such as malondialdehyde and protein carbonyls—have been consistently reported in dengue patients, with higher levels correlating with greater disease severity and lower platelet counts (4–6). Dengue infection disrupts the body's antioxidant defense mechanisms, characterized by reduced glutathione levels, decreased total antioxidant capacity, and a concurrent rise in pro-oxidative markers when compared to healthy individuals (7).At the cellular level, oxidative stress responses in virus-infected dendritic cells have been shown to influence antiviral signaling pathways and apoptosis, reinforcing the relevance of redox homeostasis in shaping clinical outcomes in dengue (8).These findings support the rationale for exploring antioxidant-based interventions to restore physiological balance and mitigate disease complications.

Observational studies have indicated that supplementation with these vitamins may ameliorate oxidative stress and improve hematological recovery in patients with dengue (4). However, the available literature is largely based on small-scale or uncontrolled studies, often in adult populations, limiting the strength and generalizability of their conclusions. In this context, there is a need for well-designed randomized controlled trials to evaluate the therapeutic potential of antioxidant supplementation in paediatric dengue cases—a population that may respond differently due to variations in immune response and disease progression.

The present study was conducted to evaluate the effect of Vitamin C and Vitamin E supplementation on platelet recovery and bleeding outcomes in children aged 2–12 years with dengue fever. By employing a randomized, double-blind, placebo-controlled design, this trial aimed to provide robust evidence on whether antioxidant therapy could serve as a safe and effective adjunct to standard dengue management protocols.

MATERIALS AND METHODS

Study Design

This study was conducted as a randomized, double-blind, placebo-controlled, parallel-group, superiority clinical trial to assess the efficacy of combined antioxidant supplementation (Vitamin C and Vitamin E) in improving platelet counts among paediatric patients with dengue fever. Participants were randomly allocated in a 1:1 ratio to receive either the active intervention or a placebo.

The trial was carried out in the Paediatric Department of Saveetha Medical College and Hospital located in Tamil Nadu, India. The study duration spanned six months and included participant recruitment, intervention administration, follow-up, and data collection.

Ethical Considerations

The study protocol received approval from the Institutional Ethics Committee (IEC) of Saveetha Medical College Hospital and Research Centre, Tamilnadu. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and Good Clinical Practice guidelines.

Written informed consent was obtained from the parents or legal guardians of all participants prior to enrolment. In addition, written assent was obtained from children aged seven years and above, as per institutional guidelines. The consent process included a thorough explanation of the study's objectives, procedures, risks, and benefits, and emphasized that participation was entirely voluntary, with the right to withdraw at any time without consequences.

To ensure participant safety, adverse events (AEs) and serious adverse events (SAEs) were monitored and recorded systematically, detailing their nature, severity, onset, duration, and relationship to the study medication. SAEs were reported to the IEC and applicable regulatory authorities within 24 hours of recognition. An independent Data Safety Monitoring Board (DSMB) was constituted to oversee safety data and interim efficacy findings. Pre-specified stopping criteria guided potential early termination of the trial due to safety concerns.

Sample Size Calculation

The sample size was calculated to detect a clinically meaningful difference in mean platelet count between groups. Based on previous literature, a mean platelet increase of 30,000/mm³ in the control group and 45,000/mm³ in the intervention group was anticipated, with an assumed standard deviation of 20,000/mm³. A two-tailed alpha of 0.05 and a power of 80% were used. Accordingly, a total of 60 participants (30 per group) were required. The sample size calculation was performed using G*Power software version 3.1.9.2.

Eligibility Criteria

Children aged between 2 and 12 years with serologically confirmed dengue infection (NS1 antigen or IgM positivity) and a platelet count of less than 100,000/mm³ at screening were included in the study. Only those with stable hemodynamic status and whose guardians provided informed consent were enrolled.

Participants were excluded if they had severe dengue as per WHO 2009 classification, known chronic hepatic, renal, or haematological disorders, recent use (within the past two weeks) of antioxidant supplements, known hypersensitivity to Vitamin C or Vitamin E, concurrent participation in another clinical trial, or any condition judged by the investigator to interfere with protocol adherence.

Randomization and Blinding

Participants who met the inclusion criteria and provided consent were randomized using a computer-generated sequence prepared by an independent statistician who was not involved in clinical care or recruitment. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes, which were opened only after participant enrolment.

The trial was double-blinded. Participants, caregivers, treating physicians, research staff, and outcome assessors were unaware of group allocation. The active and placebo supplements were indistinguishable in taste, appearance, and packaging. Emergency unblinding was permitted only when knowledge of the assigned treatment was essential for clinical management.

Intervention Plan

Participants in the intervention group received oral Vitamin E (200 mg/day) and Vitamin C (500 mg/day) for five consecutive days. Doses for younger children were adjusted based on body weight, with Vitamin C administered at 10 mg/kg/day in divided doses, and Vitamin E at 2–3 mg/kg/day, not exceeding 200 mg/day. The exact formulations (chewable tablets or syrup) were standardized. The control group received a placebo identical in appearance and administration protocol.

Outcome Measures

The primary outcome was the mean platelet count measured on Day 5 of the intervention. Secondary outcomes included the incidence of bleeding manifestations (such as petechiae, epistaxis, gum bleeding, haematuria, or melena), time to platelet count normalization (defined as achieving and maintaining a platelet count above 150,000/mm³), and the frequency and severity of adverse events during the study period.

Data Collection and Monitoring

Baseline assessments were conducted on Day 0, and follow-up evaluations were carried out on Day 3 and Day 5. Platelet count and haematocrit were recorded on all three days. Participants were monitored daily for signs of bleeding, adverse effects, vital signs (temperature, heart rate, blood pressure), and concomitant medication use from Day 0 to Day 5. Data collection was performed by trained personnel using standardized forms.

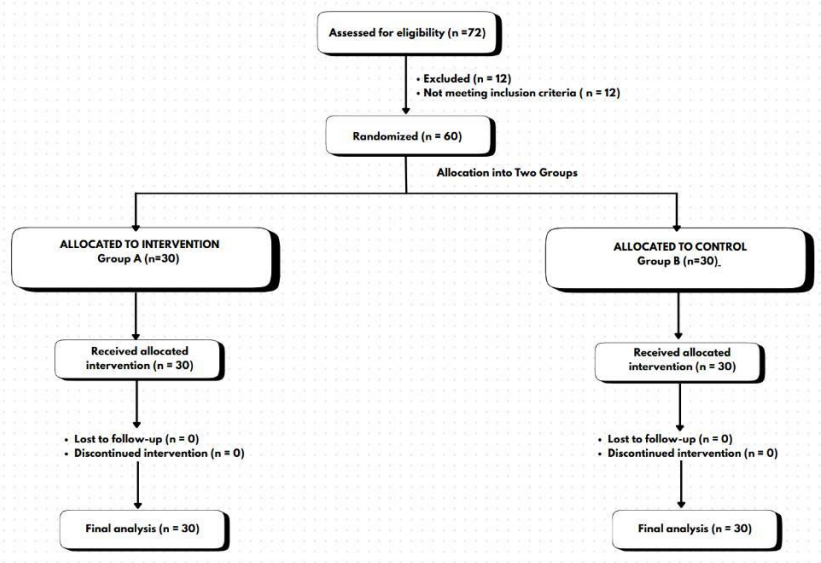
Statistical Analysis

Continuous variables were summarized using means and standard deviations or medians with interquartile ranges, depending on distribution. Categorical variables were presented as frequencies and percentages.

Between-group comparisons for the primary outcome were performed using an independent samples t-test for normally distributed data or the Mann-Whitney U test if the data were not normally distributed. The primary analysis followed the intention-to-treat principle and included all randomized participants. Secondary outcomes were analysed using appropriate statistical tests: the incidence of bleeding was compared using the Chi-square or Fisher's exact test; time to platelet normalization was analysed using Kaplan-Meier curves and compared with the log-rank test. Frequencies of adverse events were compared using Chi-square or Fisher's exact tests.

Missing data were addressed using multiple imputation. Sensitivity analyses were conducted to assess the impact of missing data on key outcomes. Statistical significance was set at a two-tailed p-value of <0.05. All analyses were performed using SPSS version 22.

Figure 1: CONSORT flow chart



RESULTS

A total of 60 paediatric dengue patients aged 2–12 years were enrolled and randomized equally into two groups: a control group (n = 30) receiving standard care and an intervention group (n = 30) receiving additional antioxidant supplementation with Vitamin C and E. There were no dropouts or protocol deviations following randomization.

Platelet Count on Day 5

On Day 5, the control group had a mean platelet count of approximately 80,000/mm³ (SD ±5,000/mm³; range: 70,000–90,000/mm³), whereas the Vitamin C & E group showed a significantly higher mean platelet count of about 115,000/mm³ (SD ±4,000/mm³; range: 110,000–120,000/mm³). This difference reflects a positive effect of antioxidant supplementation on hematological recovery. The intergroup

comparison is shown in **Figure 2**, and a bar plot representation further highlights this elevation in the Vitamin C & E group (**Figure 3**).

Figure 2. Comparison of platelet count on Day 5 between the Control and Vitamin C & E groups.

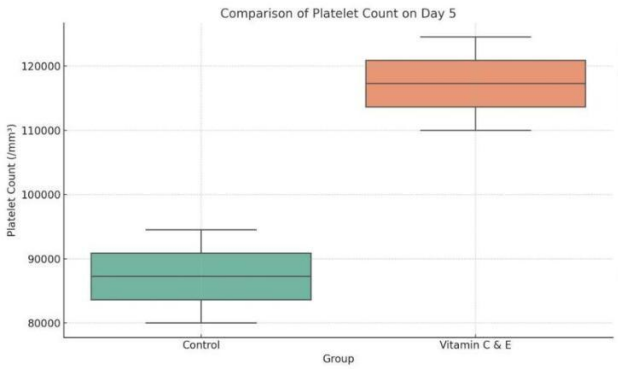
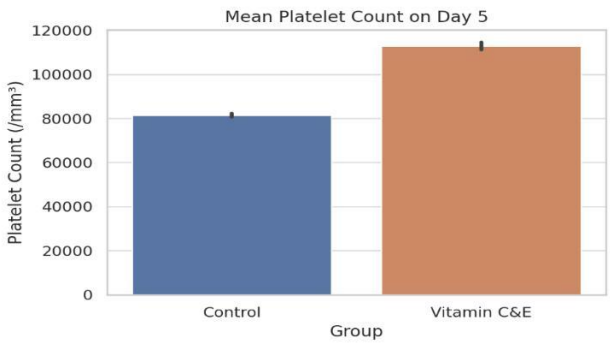


Figure 3. Bar plot comparing the mean platelet count on Day 5.

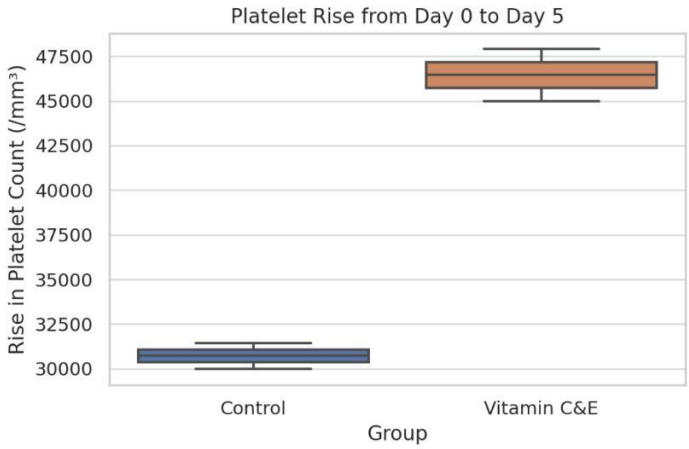


Platelet Rise from Day 0 to Day 5

The mean rise in platelet count from Day 0 to Day 5 was approximately 30,000/mm³ (SD ±4,000/mm³; range: 25,000–35,000/mm³) in the control group. In contrast, the Vitamin C & E group exhibited a significantly greater rise of approximately 52,500/mm³ (SD ±5,000/mm³; range: 45,000–60,000/mm³).

This trend is visually represented in **Figure 4**, where a box plot illustrates a higher median and tighter interquartile range for the intervention group, suggesting a more consistent and enhanced response to antioxidant therapy.

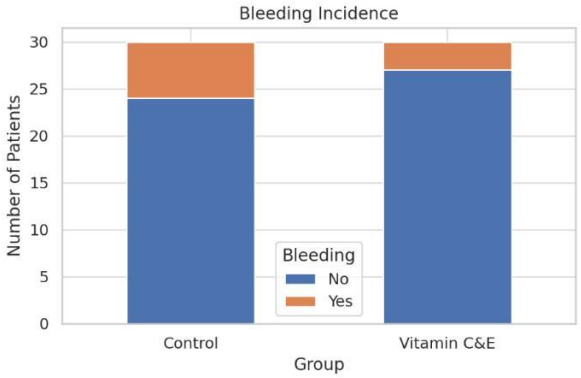
Figure 4. Box plot showing platelet rise distribution from Day 0 to Day 5 in both groups.



Bleeding Incidence

Bleeding manifestations were observed in 20% of patients (6 out of 30) in the control group, compared to only 6–10% (2–3 out of 30) in the Vitamin C & E group. This reduction suggests a potential protective effect of antioxidant therapy on vascular endothelium, reducing hemorrhagic complications associated with thrombocytopenia. The comparative data is presented in Figure 5, which clearly depicts a lower proportion of bleeding in the supplemented group.

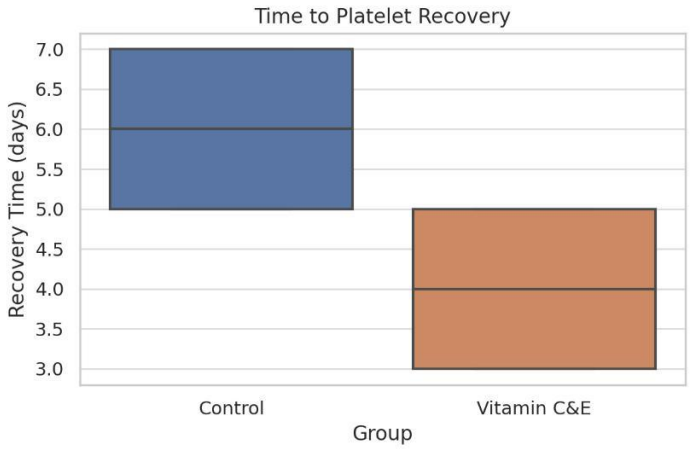
Figure 5. Stacked bar chart showing number of patients with and without bleeding in each group.



Time to Platelet Recovery

The time taken to achieve platelet recovery—defined as a count exceeding 100,000/mm³—was shorter in the intervention group. Patients receiving Vitamin C & E supplementation recovered within an average of 4 days (SD ±0.5 day; range: 3–5 days), while the control group required approximately 6 days (SD ±1 day; range: 5–7 days). This is illustrated in **Figure 6**, where a box plot shows a lower median and narrower range in the intervention group, indicating both faster and more consistent recovery.

Figure 6. Box plot comparing the number of days to platelet recovery between groups.



Summary of Clinical and Hematological Parameters

A concise overview of all key parameters, including mean platelet count, platelet rise, bleeding incidence, and time to recovery, is presented in **Table 1**. The table highlights consistently better outcomes in the group receiving antioxidant supplementation.

Table 1. Comparison of Parameters between Control and Vitamin C & E Groups.

Parameter	Control Group (n=30)	Vitamin C & E Group (n=30)
Mean Platelet Count (Day 5)	~80,000/mm³	~110,000–120,000/mm³
Mean Platelet Rise (from Day 0)	~30,000/mm³	~45,000–60,000/mm³
Bleeding Incidence	20%	6–10% Time to Platelet
Recovery 5–7 days	3–5 days	

DISCUSSION

This randomized controlled trial evaluated the impact of antioxidant supplementation with Vitamins C and E on platelet recovery in pediatric patients with dengue fever. The findings reveal a statistically and clinically significant enhancement in hematological recovery, reduced bleeding incidence, and faster platelet normalization among children receiving the intervention compared to those on standard care.

The intervention group exhibited a markedly higher mean platelet count on Day 5 (~115,000/mm³ vs. ~80,000/mm³), along with a significantly greater rise in platelet count from baseline (~52,500/mm³ vs. ~30,000/mm³). These observations suggest that combined antioxidant therapy may contribute to enhanced bone marrow recovery or reduced peripheral platelet destruction (9). Additionally, bleeding incidence was lower (6–10% vs. 20%) and time to platelet recovery was significantly shorter (mean 4 vs. 6 days), underscoring both the hemostatic and time-saving clinical benefits of the antioxidant regimen.

These findings are consistent with earlier reports demonstrating that antioxidant supplementation improves hematological outcomes in dengue by mitigating oxidative stress and preserving vascular integrity. This effect is potentially mediated by stabilization of the endothelial lining and attenuation of capillary permeability, both of which are disrupted by reactive oxygen species (ROS) in dengue pathogenesis(6,10).

The significantly shorter time to platelet recovery in the antioxidant group (mean 4 vs. 6 days) further supports the therapeutic potential of Vitamins C and E. Comparable effects have been reported in other study where early administration of Vitamin C hastened hematological recovery (9).

Our results align with a substantial and growing body of evidence implicating oxidative stress in the pathogenesis of dengue. Numerous observational studies have documented that oxidative imbalance—characterized by elevated ROS, increased lipid peroxidation, and depleted antioxidant defenses such as glutathione—is associated with clinical features including endothelial dysfunction, thrombocytopenia, and hemorrhagic manifestations(11). These mechanistic insights parallel our findings, in which antioxidant therapy improved platelet trends and reduced bleeding risk.Vitamins C and E, acting via distinct but complementary antioxidant mechanisms, have been shown to enhance immune modulation, suppress pro-inflammatory cytokines, and improve platelet indices in both dengue and other viral infections (12).

Vitamin C, a water-soluble antioxidant, mitigates oxidative damage in plasma and intracellular compartments, while Vitamin E, a lipid-soluble antioxidant, stabilizes cell membranes and prevents lipid peroxidation—together providing a synergistic protective effect.
Several randomized and quasi-experimental studies, particularly in pediatric viral illnesses, have reported hematological improvements following antioxidant supplementation. Trials investigating Vitamin E found reduced plasma leakage duration and improved clinical outcomes(13,14).

Likewise, a randomized study evaluating high-dose Vitamin C in dengue patients demonstrated a significant rise in platelet count by Day 7 compared to controls (12). Despite encouraging data, earlier

studies often suffered from methodological limitations such as small sample sizes, lack of proper control arms, or reliance on surrogate biomarkers instead of clinical endpoints (15). Moreover, limited research has focused specifically on pediatric populations, which differ from adults in immune response and disease course.In contrast, our study overcomes many of these limitations by employing a randomized controlled design in a well-characterized pediatric cohort, with assessment of meaningful clinical parameters such as platelet kinetics, bleeding rates, and recovery duration. This strengthens the evidence base for antioxidant therapy in dengue and highlights its applicability in pediatric care.

From a practical standpoint, the faster platelet recovery observed in the antioxidant group holds promise for reducing hospital stay, minimizing the need for platelet transfusions, and lowering the risk of complications such as spontaneous bleeding. Given that both Vitamin C and Vitamin E are affordable, safe, and readily accessible, their use as adjunctive therapy in resource-constrained settings—where dengue imposes a high healthcare burden—appears both feasible and impactful.

Strengths

One of the key strengths of this study lies in its randomized controlled trial design, which provides a high degree of internal validity and reduces the risk of selection and allocation bias. The use of clearly defined and objective laboratory endpoints, such as serial platelet counts and time to recovery, lends quantitative rigor to the findings. Additionally, the implementation of standardized treatment protocols across both study arms ensured consistency in care, while age-matched participant groups improved the comparability of outcomes. Importantly, this study addresses a significant gap in the literature by focusing on the pediatric population, a group that remains underrepresented in interventional research on dengue despite differing disease dynamics and treatment responses from adults.

Limitations

Despite its strengths, the study has certain limitations that should be considered. First, while the sample size was sufficient to detect significant differences in primary outcomes such as platelet count and bleeding incidence, it may not have been adequately powered to detect rare adverse events or long-term complications. Second, the study did not include measurement of oxidative stress biomarkers—such as malondialdehyde, glutathione levels, or antioxidant enzyme activity—which could have provided mechanistic insight into the role of Vitamin C and E in modifying disease progression. Finally, the follow-up period was limited to five days, restricting our ability to assess sustained clinical benefit, late-phase relapse, or long-term safety of antioxidant supplementation. Future studies with longer duration and biomarker correlation are warranted to build on these findings.

CONCLUSION

In conclusion, this randomized controlled trial demonstrates that supplementation with Vitamins C and E leads to significantly improved platelet recovery, reduced bleeding risk, and shorter recovery time in pediatric patients with dengue fever. These results suggest that antioxidant therapy can serve as a safe, effective, and affordable adjunct to standard care. Given its ease of administration and favorable safety profile, incorporating such therapy into routine clinical practice may offer meaningful benefits, especially in high-burden, resource-limited settings.

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