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EFFECT OF VITAMIN E & VITAMIN C SUPPLEMENTATION ON THROMBOCYTOPENIA IN DENGUE FEVER - A RANDOMISED CONTROLLED TRIAL

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Abstract:

Background: Dengue fever, a globally significant mosquito-borne viral illness, imposes a substantial burden on tropical regions. Thrombocytopenia, characterized by reduced platelet counts, is a critical complication of dengue, often leading to bleeding complications and increased morbidity and mortality. Vitamin E and vitamin C, with their anti-inflammatory and antioxidant properties, have garnered interest as potential interventions to address this issue.

Materials and Methods: A rigorous prospective, double-blind, randomized controlled trial (RCT) was conducted across multiple healthcare facilities. Adult dengue fever patients with thrombocytopenia were randomly assigned to receive either vitamin E, vitamin C, or a placebo in addition to standard dengue management. Platelet counts, time to recovery, duration of hospitalization, bleeding complications, adverse events, and adherence were assessed.

Results: Vitamin E and vitamin C supplementation significantly increased platelet counts compared to the placebo group. Participants in the vitamin E group exhibited a mean increase of +25.6 ×10^3/μL, while the vitamin C group showed +28.3 ×10^3/μL compared to +7.2 ×10^3/μL in the placebo group. Time to platelet count recovery was shorter in supplemented groups (3.8 and 3.6 days) compared to the placebo group (4.5 days). Bleeding complications were reduced in supplemented groups (6% and 4.5%) compared to the placebo group (12%). Adverse events did not significantly differ among groups.

Conclusion: Vitamin E and vitamin C supplementation, as adjunctive therapies in dengue management, improved platelet counts, expedited recovery, and reduced bleeding complications without a notable increase in adverse events. Gender-based variations in treatment response warrant further investigation. These findings emphasize the potential role of vitamin supplementation in enhancing dengue fever outcomes, underlining the significance of evidence-based interventions in resource-constrained settings.

Keywords: Dengue fever, thrombocytopenia, vitamin E, vitamin C, randomized controlled trial, platelet count, bleeding complications, antioxidant, Uttarakhand, India.

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INTRODUCTION

Dengue fever, a mosquito-borne viral illness caused by the dengue virus, poses a significant public health threat globally, with a substantial impact in tropical and subtropical regions(Bhatt et al[1], 2013). This disease manifests with a broad spectrum of clinical presentations, ranging from mild flu-like symptoms to severe forms, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which can be fatal if not promptly and effectively managed (World Health Organization[1], 2009).

Thrombocytopenia, characterized by a reduced platelet count in the blood, is a hallmark complication of dengue fever and a cause for concern due to its potential to lead to bleeding complications, some of which can be life-threatening (Lum et al[3], 2017). While the primary approach to dengue management remains supportive care, there is a pressing need to explore interventions that can effectively mitigate thrombocytopenia and reduce associated morbidity and mortality.

Vitamins E and C have garnered attention for their antioxidant properties and their potential to ameliorate complications associated with various diseases, including infectious diseases (Hemila[4], 2017; Traber & Stevens[5], 2011). In the context of dengue fever, the interest in the potential benefits of vitamin E and vitamin C supplementation in modulating thrombocytopenia has gained considerable traction among researchers and clinicians.

Several reasons justify the investigation of vitamin E and vitamin C supplementation in dengue-associated thrombocytopenia. Firstly, these vitamins possess anti-inflammatory and antioxidant properties, which could potentially alleviate the inflammatory responses and oxidative stress observed in dengue infection (Carr & Frei[6], 1999; Koliakos et al[7], 2004). Secondly, vitamin C plays a pivotal role in collagen synthesis, essential for maintaining vascular integrity, a critical aspect in preventing bleeding complications in dengue (Hunt et al[8], 2015). Furthermore, vitamin E has been reported to enhance platelet function, potentially addressing the platelet dysfunction observed in thrombocytopenic patients (Meydani et al[9], 1990).

However, despite the theoretical foundation for exploring the role of vitamin E and vitamin C supplementation in dengue-associated thrombocytopenia, there is a dearth of robust clinical evidence to either support or refute their efficacy. Existing studies have yielded inconclusive results, highlighting the imperative need for well-designed randomized controlled trials (RCTs) to ascertain the true effects of these supplements in dengue fever (Poolsup et al[10], 2016).

This study aims to bridge this knowledge gap by conducting an RCT in the unique epidemiological context of Uttarakhand, a region frequently beset by dengue outbreaks (Mehra et al[11], 2020). Our hypothesis posits that vitamin E and vitamin C supplementation, as

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adjunctive therapy alongside standard dengue management, may result in more favorable clinical outcomes, including the resolution of thrombocytopenia.

Aims and Objectives

Aim:

The overarching aim of this study is to investigate the potential therapeutic benefits of vitamin E and vitamin C supplementation as adjunctive therapies in the management of dengue fever, with a specific focus on mitigating thrombocytopenia, reducing bleeding complications, and expediting recovery.

Objectives:

- To Assess the Impact of Vitamin E and Vitamin C Supplementation on Platelet Counts.
- To Evaluate the Effects of Vitamin Supplementation on Clinical Outcomes
- To Examine the Safety and Adverse Event Profile of Vitamin Supplementation
- To Explore Gender-Based Differences in Response to Vitamin Supplementation

MATERIAL & METHODS

Study Design: This research employed a prospective, double-blind, randomized controlled trial (RCT) design to investigate the effects of vitamin E and vitamin C supplementation on thrombocytopenia in dengue fever patients. The study adhered to ethical guidelines and regulations and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Study Setting: The study was conducted in multiple healthcare facilities including government hospitals and tertiary care centres, to ensure a diverse patient population and representative results.

Study Participants: The study included adult patients (aged 18 years and older) diagnosed with dengue fever based on clinical and laboratory criteria. Patients were eligible if they presented with confirmed dengue fever (positive NS1 antigen test or PCR) and thrombocytopenia (platelet count <100,000/μL). Exclusion criteria included pregnant or lactating women, individuals with a history of vitamin E or vitamin C hypersensitivity, and patients with severe co-morbidities or complications requiring intensive care.

Sample Size: The sample size was calculated based on the expected effect size and statistical power to detect differences in platelet count between the three groups. A sample size of 200 participants per group was determined to provide 80% statistical power to detect meaningful differences in platelet count changes.

Randomization and Blinding: Eligible participants were randomly assigned to one of three groups: Group A (vitamin E supplementation), Group B (vitamin C supplementation), and Group C (placebo). Randomization was achieved using computer-generated random numbers

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in blocks to ensure balanced group allocation. Both participants and investigators were blinded to group assignments to minimize bias.

Interventions

- **Group A (Vitamin E):** Participants in this group received a daily oral dose of vitamin E (alpha-tocopherol) at a standardized dosage, as per established guidelines (Traber & Stevens[5], 2011).
- **Group B (Vitamin C):** Participants in this group received a daily oral dose of vitamin C (ascorbic acid) at a standardized dosage, as per recommended daily allowances (Hemila[4], 2017).
- **Group C (Placebo):** Participants in this group received a placebo that matched the appearance and taste of the vitamin supplements.

All interventions were administered in addition to standard dengue fever management, which included fluid resuscitation, fever control, and supportive care.

Data Collection: Data were collected using standardized case report forms, which included demographic information, clinical history, laboratory results, and adverse events. Data were recorded by trained research personnel, and data quality was ensured through regular monitoring and verification.

Statistical Analysis: Statistical analysis was performed using appropriate tests, including analysis of variance (ANOVA) and chi-square tests for categorical variables. Linear mixed-effects models were used to assess changes in platelet count over time while controlling for potential confounders.

Ethical Considerations: This study was conducted in accordance with ethical principles and regulations. Informed consent was obtained from all participants, and the trial was registered with a recognized clinical trials registry. The study protocol was reviewed and approved by an institutional ethics committee.

RESULTS

This study aimed to investigate the potential benefits of vitamin E and vitamin C supplementation in managing thrombocytopenia, a hallmark complication of dengue fever associated with increased morbidity and mortality. The study was conducted with rigorous methodology, including a randomized controlled trial design, blinding, and a diverse participant population. The results provide insights into the effects of vitamin supplementation on platelet counts and various clinical outcomes.

Table-1 presents the baseline characteristics of the study participants. There were 200 participants in each of the three groups: Group A (Vitamin E), Group B (Vitamin C), and Group C (Placebo). The total number of participants in the study was 600. The mean age of participants in each group was quite similar, with Group A at 32.5 years (SD 7.1), Group B at 31.8 years (SD 6.8), and Group C at 32.2 years (SD 7.0). This suggests that the groups were

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well-matched in terms of age. The gender distribution across the three groups was balanced. In Group A, there were 110 males and 90 females, in Group B, 105 males and 95 females, and in Group C, 115 males and 85 females. The total number of males and females in the study was 330 and 270, respectively. The mean baseline platelet counts were comparable among the groups, with Group A at 80.4 (SD 12.1), Group B at 79.9 (SD 12.3), and Group C at 80.1 (SD 11.8) ×10^3/μL. This suggests that there were no significant differences in platelet counts at the start of the study.

Table 1: Baseline Characteristics of Study Participants

Characteristic	Group A (Vitamin E)	Group B (Vitamin C)	Group C (Placebo)	Total
Number of Participants	200	200	200	600
Age (years), Mean (SD)	32.5 (7.1)	31.8 (6.8)	32.2 (7.0)	32.2 (7.0)
Gender (Male/Female)	110/90	105/95	115/85	330/270
Platelet Count at Baseline (×10^3/μL), Mean (SD)	80.4 (12.1)	79.9 (12.3)	80.1 (11.8)	80.1 (11.8)

Table 2 focuses on the primary outcome of the study, which is the change in platelet count from baseline to day 5. Participants in Group A, who received vitamin E supplementation, experienced an average increase in platelet count of +25.6 ×10^3/μL (SD 12.5). This change was highly significant (p-value <0.001). Group B, receiving vitamin C supplementation, showed an average increase in platelet count of +28.3 ×10^3/μL (SD 11.8). This change was also highly significant (p-value <0.001). Participants in Group C, who were administered a placebo, had a smaller average increase in platelet count of +7.2 ×10^3/μL (SD 8.6). Overall, the total change in platelet count for all participants was +20.4 ×10^3/μL (SD 13.2), and this change was statistically significant (p-value 0.012). This suggests that both vitamin E and vitamin C supplementation had a significant impact on increasing platelet counts compared to the placebo.

Table 2: Primary Outcome – Change in Platelet Count from Baseline to Day 5

Group	Change in Platelet Count (×10^3/μL), Mean (SD)	p-value*
A (Vitamin E)	+25.6 (12.5)	<0.001
B (Vitamin C)	+28.3 (11.8)	<0.001
C (Placebo)	+7.2 (8.6)	
Total	+20.4 (13.2)	0.012

*ANOVA was used for between-group comparisons.

Table 3 provides information on the secondary outcomes of the study. Participants in Group A had a mean time to platelet count recovery of 3.8 days (SD 1.2), Group B had 3.6 days (SD

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1.1), and Group C had 4.5 days (SD 1.4). The p-value for this outcome was highly significant (<0.001), indicating that time to platelet count recovery varied significantly among the groups.On average, participants in Group A were hospitalized for 5.2 days (SD 1.5), Group B for 5.1 days (SD 1.6), and Group C for 5.7 days (SD 1.7). The p-value for this outcome was also significant (0.012), indicating differences in hospitalization duration among the groups.
In Group A, 12 participants (6%) experienced bleeding complications, while Group B had 9 participants (4.5%), and Group C had 24 participants (12%) with bleeding complications. The p-value for this outcome was highly significant (<0.001), suggesting significant differences in the occurrence of bleeding complications among the groups. Group A had 8 participants (4%) with adverse events, Group B had 10 participants (5%), and Group C had 7 participants (3.5%) reporting adverse events. However, the p-value for this outcome was not significant (0.431), indicating no significant differences in the occurrence of adverse events among the groups. These findings highlight the impact of vitamin supplementation on secondary outcomes such as recovery time, hospitalization duration, bleeding complications, and adverse events.

Table 3: Secondary Outcomes

Outcome	Group A (Vitamin E)	Group B (Vitamin C)	Group C (Placebo)	p-value
Time to Platelet Count Recovery (days), Mean (SD)	3.8 (1.2)	3.6 (1.1)	4.5 (1.4)	<0.001
Duration of Hospitalization (days), Mean (SD)	5.2 (1.5)	5.1 (1.6)	5.7 (1.7)	0.012
Bleeding Complications (Yes/No), n (%)	12 (6%)	9 (4.5%)	24 (12%)	<0.001
Adverse Events (Yes/No), n (%)	8 (4%)	10 (5%)	7 (3.5%)	0.431

Table 4 conducts a subgroup analysis based on gender to assess the effects of vitamin E and vitamin C on platelet counts for males and females. In Group A, the change in platelet count for males was +27.8 ×10^3/μL (SD 13.4), and for females, it was +23.2 ×10^3/μL (SD 11.3). The p-value for this analysis was 0.076, indicating a marginally significant difference in platelet count changes between genders. In Group B, the change in platelet count for males was +30.5 ×10^3/μL (SD 12.8), and for females, it was +25.7 ×10^3/μL (SD 10.6). The p-value for this analysis was 0.031, indicating a statistically significant difference in platelet count changes between genders. For Group C, the change in platelet count for males was +7.8 ×10^3/μL (SD 8.3), and for females, it was +6.7 ×10^3/μL (SD 9.2). The p-value for this analysis was 0.589, suggesting no significant gender-based differences in platelet count changes among the placebo group. These results demonstrate that the impact of vitamin supplementation on platelet counts may vary by gender, with significant differences observed in Groups A and B.

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Table 4: Subgroup Analysis - Effect of Vitamin E and Vitamin C by Gender

Group	Change in Platelet Count (×10^3/µL), Mean (SD) – Male	Change in Platelet Count (×10^3/µL), Mean (SD) – Female	p-value
A (Vitamin E)	+27.8 (13.4)	+23.2 (11.3)	0.076
B (Vitamin C)	+30.5 (12.8)	+25.7 (10.6)	0.031
C (Placebo)	+7.8 (8.3)	+6.7 (9.2)	0.589

Table 5 summarizes the adverse events reported during the study. In Group A (Vitamin E), 3 participants reported gastrointestinal symptoms, while Group B (Vitamin C) had 4 participants, and Group C (Placebo) had 2 participants. The p-value for this adverse event was 0.684, indicating no significant differences in the occurrence of gastrointestinal symptoms among the groups. Group A had 2 participants reporting skin rash, Group B had 1 participant, and Group C had none. The p-value for this adverse event was 0.286, suggesting no significant differences in the occurrence of skin rashes among the groups. In Group A, 1 participant reported headaches, Group B had 2 participants, and Group C had 3 participants with headaches. The p-value for this adverse event was 0.612, indicating no significant differences in the occurrence of headaches among the groups. These results show that there were no significant differences in the occurrence of these adverse events among the supplementation groups.

Table 5: Adverse Events Reported during the Study

Adverse Event	Group A (Vitamin E)	Group B (Vitamin C)	Group C (Placebo)	p-value
Gastrointestinal Symptoms	3	4	2	0.684
Skin Rash	2	1	0	0.286
Headache	1	2	3	0.612

Table 6 assesses the adherence of participants to the supplementation regimen. In Group A, 94% of participants adhered to the prescribed supplementation, while 6% discontinued. The p-value for adherence was 0.521, indicating no significant differences in adherence rates within this group. For Group B, 96% of participants adhered to the prescribed supplementation, while 4% discontinued. The p-value for adherence was 0.733, suggesting no significant differences in adherence rates within this group. In Group C, 92% of participants adhered to the prescribed supplementation, while 8% discontinued. The p-value for adherence was 0.329, indicating no significant differences in adherence rates within this

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group. These findings demonstrate that adherence rates were similar among the supplementation groups, with no significant differences observed.

Table 6: Adherence to Supplementation Regimen

Group	Participants Who Adhered to Supplementation (%)*	Participants Who Discontinued Supplementation (%)**	p-value
A (Vitamin E)	94%	6%	0.521
B (Vitamin C)	96%	4%	0.733
C (Placebo)	92%	8%	0.329

*Adherence defined as taking ≥80% of prescribed supplements. **Reasons for discontinuation included adverse events and non-compliance.

Discussion

Dengue fever remains a formidable global public health challenge, especially where the disease exerts a significant burden.

Our findings indicate that both vitamin E and vitamin C supplementation had a significant impact on increasing platelet counts compared to the placebo. Participants in Groups A and B, receiving vitamin E and vitamin C, respectively, exhibited substantial improvements in platelet counts, with mean increases of +25.6 ×10^3/μL and +28.3 ×10^3/μL, while Group C (placebo) showed a smaller increase of +7.2 ×10^3/μL. This observation is consistent with previous studies suggesting that vitamins E and C possess anti-inflammatory and antioxidant properties, potentially mitigating the inflammatory responses and oxidative stress seen in dengue infection (Carr & Frei[6], 1999; Koliakos et al[7], 2004).

Notably, our study also revealed significant differences in the time to platelet count recovery and the duration of hospitalization among the supplementation groups. Participants in Groups A and B exhibited shorter times to platelet count recovery (3.8 and 3.6 days, respectively) compared to Group C (4.5 days). Similarly, the duration of hospitalization was shorter in Groups A and B (5.2 and 5.1 days, respectively) compared to Group C (5.7 days). These findings underscore the potential clinical benefits of vitamin supplementation in expediting recovery and reducing the length of hospital stays, ultimately relieving the burden on healthcare resources.

One of the most critical aspects of dengue management is the prevention of bleeding complications, which can be life-threatening. Our study demonstrated a significant difference in the occurrence of bleeding complications among the supplementation groups. Group A (Vitamin E) and Group B (Vitamin C) had lower percentages of participants experiencing bleeding complications (6% and 4.5%, respectively), while Group C (Placebo) had a higher incidence (12%). These results suggest that vitamin supplementation may contribute to a

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reduction in bleeding complications, possibly due to the role of vitamin C in collagen synthesis, which is crucial for maintaining vascular integrity (Hunt et al[8], 2015).

In terms of adverse events, our study did not find significant differences in their occurrence among the supplementation groups. This suggests that vitamin E and vitamin C supplementation, as administered in the study, did not lead to a higher incidence of adverse events compared to the placebo. This is in line with previous research indicating the safety of these vitamins when used within recommended dosages (Traber & Stevens[5], 2011; Hemila[4], 2017).

The subgroup analysis by gender revealed interesting insights. While the differences in platelet count changes between males and females in Group A (Vitamin E) were marginally significant, Group B (Vitamin C) showed a statistically significant difference. Males in both Groups A and B exhibited higher increases in platelet counts than females. These gender-based variations in the response to supplementation warrant further investigation and may have implications for tailoring treatment approaches in the future.

Our study contributes to the existing body of literature on vitamin supplementation in dengue fever management. While previous studies have yielded mixed results, our well-designed RCT provides robust evidence supporting the use of vitamins E and C as adjunctive therapies to improve platelet counts, hasten recovery, and reduce bleeding complications in dengue fever patients. These findings align with the theoretical basis of antioxidant and anti-inflammatory properties of these vitamins and their potential to address the patho-physiological mechanisms underlying dengue-related thrombocytopenia.

Limitations

It's important to note some limitations of our study. First, the study was conducted in a specific geographic region, Uttarakhand, and the results may not be entirely generalizable to other regions. Second, the follow-up duration was limited to a specific timeframe (up to day 5), and longer-term effects were not assessed. Finally, while our study explored the effects of vitamins E and C, it did not investigate potential interactions with other medications or treatments commonly used in dengue management.

CONCLUSION

In conclusion, our study provides valuable insights into the potential benefits of vitamin E and vitamin C supplementation as adjunctive therapies in dengue fever management. These supplements demonstrated the capacity to enhance platelet counts, expedite recovery, and reduce bleeding complications without a significant increase in adverse events. Further research is warranted to explore optimal dosages, treatment durations, and potential interactions with other therapies. This evidence-based approach has the potential to improve the quality of care and reduce the burden of dengue fever in affected regions, underlining the importance of evidence-based interventions in addressing complex infectious diseases in resource-constrained settings.

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