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Evaluating calcium supplementation in hypocalcemic dengue patients: A clinical study on its impact on recovery outcomes and disease severity

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Abstract

Backgrounds: Dengue fever, caused by the dengue virus, is characterized by symptoms ranging from mild fever to severe hemorrhagic manifestations. Hypocalcemia has been identified as a common biochemical abnormality in dengue patients, potentially exacerbating disease severity. This study explores the impact of calcium supplementation on clinical outcomes in hypocalcemic dengue patients. The primary objective was to assess the efficacy of calcium supplementation in improving clinical outcomes among dengue patients with hypocalcemia.

Methods: A total of 150 dengue patients at our tertiary care hospital were included in this study. Patients were categorized based on their calcium levels and disease severity. Those with moderate to severe hypocalcemia received daily oral calcium supplementation (500 mg). The duration of hospital stay and resolution of symptoms were compared between supplemented and non-supplemented groups.

Results: In a study of 150 dengue patients, 40.7% had hypocalcemia, with severe cases linked to higher incidences of DHF and DSS. Hypocalcemia patients had worse outcomes, including lower platelet counts and poorer liver and renal function. Calcium supplementation reduced hospital stays from 3.6 to 3.13 days in patients with mild hypocalcemia. The results emphasize the importance of monitoring and managing calcium levels to improve recovery and outcomes in dengue patients. These findings suggest routine calcium monitoring and early intervention could mitigate severe dengue complications.

Discussion: The study demonstrates that calcium supplementation can significantly improve clinical outcomes in dengue patients with hypocalcemia. Faster resolution of symptoms and reduced hospital stays highlight the potential benefits of incorporating calcium supplementation into the treatment regimen for hypocalcemic dengue patients.

Conclusion: Calcium supplementation in hypocalcemic dengue patients is associated with improved clinical outcomes and shorter hospital stays. This finding supports the use of calcium supplementation as a therapeutic intervention in the management of dengue fever.

Keywords: Dengue fever, hypocalcemia, calcium supplementation, clinical outcomes, hospital stay

Introduction

Dengue fever is an arthropod-borne viral infection that poses a significant global health challenge, particularly in tropical and subtropical regions^[1]. The disease is transmitted by Aedes mosquitoes, primarily *Aedes aegypti* and *Aedes albopictus*, and is caused by one of four distinct serotypes of the dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4), which belong to the Flaviviridae family^[2]. Dengue infection can lead to a wide range of clinical manifestations, from asymptomatic or mild febrile illness to severe and potentially fatal forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)^[3].

The pathogenesis of dengue is complex, involving both viral and host factors. Upon infection, the virus targets various cells, including dendritic cells, macrophages, and hepatocytes, leading to a robust immune response characterized by high levels of cytokines and chemokines^[4]. This "cytokine storm" contributes to the vascular leakage, hemorrhage, and organ dysfunction

observed in severe cases. Severe dengue is often associated with secondary infections by a different serotype, which can lead to antibody-dependent enhancement (ADE), exacerbating the disease severity [5].

Clinically, dengue fever typically presents with sudden onset of high fever, severe headache, retro-orbital pain, myalgia, arthralgia, rash, and mild bleeding manifestations such as epistaxis or gingival bleeding [6].

Severe dengue is marked by plasma leakage, severe hemorrhage, or organ involvement, manifesting as abdominal pain, persistent vomiting, rapid decline in platelet count, rise in hematocrit, and signs of circulatory failure [7].

Recent studies have identified hypocalcemia, defined as a total serum calcium level below 8.4 mg/dL, as a common biochemical abnormality in dengue patients. The prevalence of hypocalcemia in dengue ranges widely but can be as high as 40-50% in some cohorts [8]. The mechanisms leading to hypocalcemia in dengue are multifaceted, including the role of cytokines in altering calcium metabolism, the leakage of plasma calcium into interstitial spaces due to increased vascular permeability, and potential direct effects of the virus on calcium regulation [9].

Calcium plays a critical role in various physiological processes, including muscle contraction, blood coagulation, and cellular signaling. In the context of dengue, maintaining adequate calcium levels is crucial for vascular integrity and hemostasis [10]. Hypocalcemia can exacerbate the clinical course of dengue, contributing to the severity of symptoms such as hypotension, bleeding, and prolonged recovery times.

Given the high prevalence of hypocalcemia in dengue patients and its potential impact on disease severity and outcomes, calcium supplementation presents a promising therapeutic intervention. Supplementing calcium in hypocalcemic dengue patients could potentially stabilize vascular function, reduce the severity of hemorrhagic symptoms, and shorten hospital stays [11]. This study explores the impact of calcium supplementation on clinical outcomes in dengue patients with hypocalcemia, providing evidence for its potential benefits and guiding future clinical practices.

The primary objectives of this study was to determine the prevalence of hypocalcemia in patients with dengue fever. Secondly, to assess the correlation between hypocalcemia and the severity of dengue. Lastly, to evaluate the impact of calcium supplementation on clinical outcomes in hypocalcemic dengue patients. By addressing these objectives, the study aims to contribute valuable insights into the management of dengue fever and enhance patient care through targeted interventions.

Methodology

Study Design and Setting

This cross-sectional observational study was conducted at our tertiary healthcare center in India. The study spanned from October 2021 to August 2023, aiming to investigate the prevalence of hypocalcemia in dengue fever patients and the impact of calcium supplementation on clinical outcomes.

Study Population

The study included 150 patients diagnosed with dengue fever, confirmed by NS1 antigen or Dengue IgM serology. Patients were recruited from both outpatient and inpatient departments of the hospital.

The study included patients diagnosed with dengue fever by NS1 antigen or Dengue IgM serology, aged 16 years and

above. Exclusion criteria were applied to patients with autoimmune diseases, malignancy, those using medications affecting white blood cell count (Such as those for hematopoietic systemic disorders), pregnant women, and patients with concurrent infections other than dengue. This selection ensured a focused study population free from confounding factors that could influence the results.

Data Collection

Upon obtaining informed consent, each patient was followed daily during their hospital stay. Clinical and laboratory parameters recorded included vital signs (Heart rate, blood pressure), symptoms (Fever, headache, retro-orbital pain, myalgia, arthralgia), and laboratory tests (Complete blood count, platelet count, hematocrit, liver function tests, renal function tests, serum calcium levels). Additionally, abdominal ultrasound was performed to assess for signs of plasma leakage such as ascites or gallbladder edema.

Stratification and Supplementation

Patients were categorized based on the severity of dengue fever into Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) 1 & 2, DHF 3, and Dengue Shock Syndrome (DSS). Serum calcium levels were measured and hypocalcemia was classified as mild (8.0–8.39 mg/dL), moderate (7.5–7.99 mg/dL), or severe (<7.5 mg/dL). Patients with moderate to severe hypocalcemia received daily oral calcium supplementation equivalent to 500 mg of elemental calcium. Among those with mild hypocalcemia, half were randomly selected to receive calcium supplementation, while the other half did not receive supplementation until normocalcemia was achieved.

Outcome Measures

The primary outcome measure was the duration of hospital stay. Secondary outcome measures included the time to achieve normocalcemia, resolution of shock, normalization of platelet count, and resolution of transaminitis. The impact of calcium supplementation on these outcomes was analyzed.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics software (version 20.0, Chicago, IL, USA). Descriptive statistics were used to summarize demographic and clinical parameters. Continuous variables were expressed as mean with standard deviation (SD), and categorical variables were expressed as numbers and percentages. The significance of differences between groups was assessed using appropriate statistical tests, including the chi-square test for categorical variables and t-test or ANOVA for continuous variables. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants before their inclusion in the study. The study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

Results

The study included 150 patients diagnosed with dengue fever, comprising 104 males (69.3%) and 46 females (30.7%). The ages of the patients ranged from 18 to 80 years, with a mean age of 39.1±12.4 years. The mean BMI was 21.97±1.81 kg/m².

Heart rate varied between 59 to 148 beats per minute, with a mean of 89.26 ± 24.60 bpm. The average systolic blood pressure was 117.43 ± 15.65 mmHg, and the average diastolic blood pressure was 72.29 ± 10.99 mmHg. Initial mean serum calcium level at admission was 8.717 ± 0.8708 mg/dL. Other parameters recorded included a mean hematocrit of $44.27 \pm 6.033\%$, mean hemoglobin of 12.482 ± 1.2579 g/dL, and mean platelet count of $140,300 \pm 79,641$ cells/cumm (Table 1).

Hypocalcemia was detected in 40.7% of the patients. Among these, 30 patients (20%) had mild hypocalcemia, 21 patients (14%) had moderate hypocalcemia, and 10 patients (6.7%) had severe hypocalcemia. The remaining 89 patients (59.3%) had normal calcium levels (Table 2)

The study found a significant correlation between hypocalcemia and the severity of dengue fever. Among patients with severe hypocalcemia, a higher incidence of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) was observed. Specifically, 60% of patients with severe hypocalcemia had DHF 1 & 2, and 20% had DSS. In contrast, the majority of patients with normal calcium levels (71 out of 89) were diagnosed with dengue fever (DF) (Table 3).

The duration of hospital stay was shorter for patients with mild hypocalcemia who received calcium supplementation compared to those who did not receive supplementation.

Specifically, the mean hospital stay for supplemented patients was 3.13 days, whereas it was 3.6 days for non-supplemented patients, indicating a positive effect of calcium supplementation on recovery time (Table 4) (Fig 1).

The mean calcium levels varied significantly across different categories of dengue severity. Patients with dengue fever had a mean calcium level of 8.937 mg/dL, those with DHF 1 & 2 had a mean level of 8.35 mg/dL, and those with DSS had a mean level of 7.987 mg/dL. This decline in calcium levels with increasing severity of dengue underscores the importance of monitoring and managing calcium levels in these patients (Table 5).

The demographic distribution of the study population based on calcium levels showed that among the 150 dengue patients, 60 males (67.4%) and 29 females (32.6%) had normal calcium levels. In the hypocalcemic groups, mild hypocalcemia was observed in 20 males (66.7%) and 10 females (33.3%), moderate hypocalcemia in 15 males (71.4%) and 6 females (28.6%), and severe hypocalcemia in 9 males (90%) and 1 female (10%). The mean age across the groups was similar, with slight variations: normal calcium level patients had a mean age of 38.5 ± 12.1 years, mild hypocalcemia patient's 39.8 ± 11.6 years, moderate hypocalcemia patient's 40.2 ± 13.0 years, and severe hypocalcemia patient's 41.0 ± 12.8 years (Table 6).

Table 1: Demographic and Clinical parameters of study population

Parameter	Mean \pm SD (Range)	N = 150
Age (years)	39.1 \pm 12.4	18-80
BMI (kg/m ²)	21.97 \pm 1.81	18.9-29
Heart Rate (bpm)	89.26 \pm 24.60	59-148
Systolic BP (mmHg)	117.43 \pm 15.65	78-142
Diastolic BP (mmHg)	72.29 \pm 10.99	38-90
Calcium (mg/dL)	8.717 \pm 0.8708	7.2-10.7
Hematocrit (%)	44.27 \pm 6.033	33-56
Hemoglobin (g/dL)	12.482 \pm 1.2579	9.2-15.1
Platelet Count (x10 ³ /cumm)	140.3 \pm 79.641	21-430

Table 2: Prevalence of hypocalcemia in dengue patients

Calcium Level	Frequency (n)	Percentage (%)
Normal (≥ 8.4 mg/dL)	89	59.3
Mild Hypocalcemia (8.0–8.39 mg/dL)	30	20.0
Moderate Hypocalcemia (7.5–7.99 mg/dL)	21	14.0
Severe Hypocalcemia (< 7.5 mg/dL)	10	6.7
Total	150	100.0

Table 3: Severity of dengue fever and hypocalcemia

Severity of Dengue	Normal Calcium	Mild Hypocalcemia	Moderate Hypocalcemia	Severe Hypocalcemia	Total
Dengue Fever	71	18	12	2	103
DHF 1 & 2	15	8	3	6	32
DHF 3	3	4	6	2	15
Total	89	30	21	10	150

Table 4: Duration of hospital stay based on calcium supplementation in mild hypocalcemia

Group	Mean Hospital Stay (days)	Number of Patients (n)
Supplemented with Calcium	3.13	15
Not Supplemented with Calcium	3.6	15
Total	3.36	30

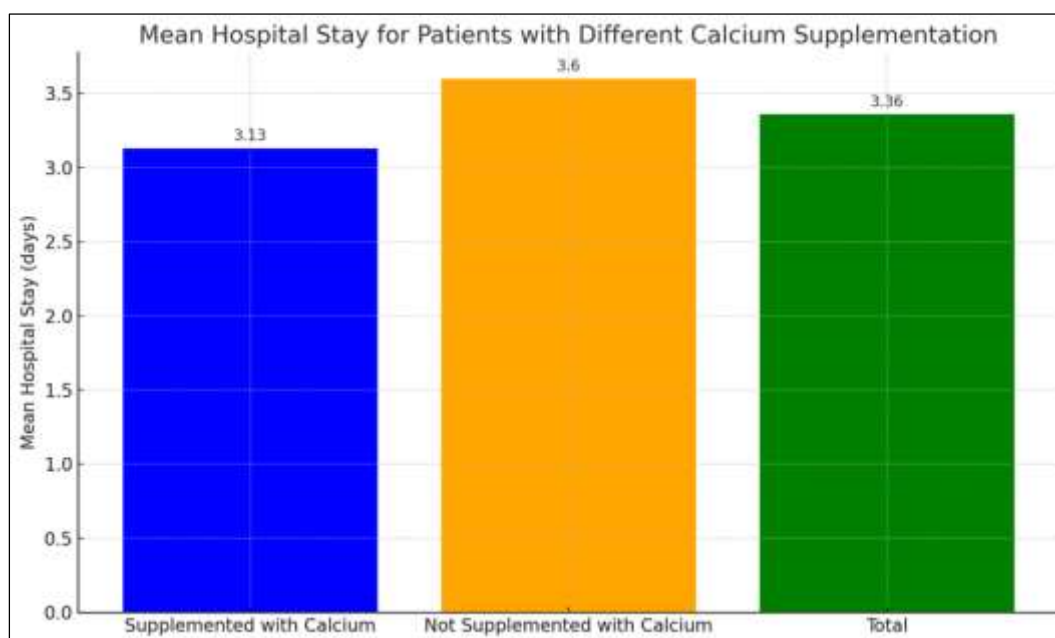


Fig 1: Mean hospital stay with and without calcium supplementation

Table 5: Mean Calcium Levels by Dengue Category

Dengue Category	Mean Calcium (mg/dL)±SD	Number of Patients (n)
Dengue Fever	8.937±0.8393	103
DHF 1 & 2	8.35±0.8144	32
DHF 3	7.987±0.4838	15
Total	8.717±0.8708	150

Table 6: Demographic Distribution by Calcium Levels

Demographic Parameter	Normal Calcium	Mild Hypocalcemia	Moderate Hypocalcemia	Severe Hypocalcemia	Total
Males	60	20	15	9	104
Females	29	10	6	1	46
Age (Mean±SD)	38.5±12.1	39.8±11.6	40.2±13.0	41.0±12.8	39.1±12.4
Total	89	30	21	10	150

Analysis of platelet counts revealed significant differences based on calcium levels. Among patients with normal calcium levels, 10 had platelet counts below $50 \times 10^3/\text{cumm}$, 20 had counts between $50-100 \times 10^3/\text{cumm}$, 25 had counts between $100-150 \times 10^3/\text{cumm}$, and 34 had counts above $150 \times 10^3/\text{cumm}$. In contrast, patients with mild hypocalcemia had higher instances of lower platelet counts: 12 had counts below $50 \times 10^3/\text{cumm}$, 10 between $50-100 \times 10^3/\text{cumm}$, 5 between $100-150 \times 10^3/\text{cumm}$, and only 3 above $150 \times 10^3/\text{cumm}$. Moderate hypocalcemia showed 8 patients with counts below $50 \times 10^3/\text{cumm}$, 7 between $50-100 \times 10^3/\text{cumm}$, 3 between $100-150 \times 10^3/\text{cumm}$, and 3 above $150 \times 10^3/\text{cumm}$. Severe hypocalcemia had the most significant impact, with 6 patients below $50 \times 10^3/\text{cumm}$, 3 between $50-100 \times 10^3/\text{cumm}$, 1 between $100-150 \times 10^3/\text{cumm}$, and none above $150 \times 10^3/\text{cumm}$ (Table 7) (Fig 2).

Liver function tests indicated worsening liver function with decreasing calcium levels. Patients with normal calcium levels had a mean AST of 45 ± 15 U/L and ALT of 40 ± 14 U/L. Those with mild hypocalcemia had higher mean AST and ALT levels (60 ± 20 U/L and 55 ± 18 U/L, respectively). Moderate hypocalcemia patients exhibited even higher levels, with AST at 75 ± 25 U/L and ALT at 70 ± 22 U/L. Severe hypocalcemia patients had the highest levels, with AST at 90 ± 30 U/L and ALT at 85 ± 28 U/L. Total and direct bilirubin levels followed a

similar trend, with increasing levels correlating with the severity of hypocalcemia (Table 8).

Renal function tests also varied with calcium levels. The mean serum creatinine for patients with normal calcium was 1.0 ± 0.2 mg/dL, which increased to 1.2 ± 0.3 mg/dL in mild hypocalcemia, 1.4 ± 0.4 mg/dL in moderate hypocalcemia, and 1.6 ± 0.5 mg/dL in severe hypocalcemia. Blood urea nitrogen (BUN) levels were similarly affected, with normal calcium patients having a mean BUN of 20 ± 6 mg/dL, which rose to 24 ± 8 mg/dL in mild hypocalcemia, 28 ± 10 mg/dL in moderate hypocalcemia, and 32 ± 12 mg/dL in severe hypocalcemia (Table 9).

Clinical outcomes were significantly influenced by the severity of hypocalcemia. Patients with normal calcium levels had the shortest mean duration to resolve shock (2.5 ± 0.5 days) and normalize platelet count (3.5 ± 0.6 days). These durations increased with the severity of hypocalcemia. For mild hypocalcemia, the mean duration to resolve shock was 3.0 ± 0.7 days and to normalize platelet count was 4.0 ± 0.8 days. Moderate hypocalcemia had a mean of 4.0 ± 0.9 days to resolve shock and 5.0 ± 1.0 days to normalize platelet count. Severe hypocalcemia patients required 5.0 ± 1.0 days to resolve shock and 6.0 ± 1.2 days to normalize platelet count. Recovery from transaminitis followed a similar pattern, with increasing duration correlating with the severity of hypocalcemia (Table 10).

Table 7: Platelet count by Calcium levels

Platelet Count (x10 ³ /cumm)	Normal Calcium	Mild Hypocalcemia	Moderate Hypocalcemia	Severe Hypocalcemia	Total
< 50	10	12	8	6	36
50-100	20	10	7	3	40
100-150	25	5	3	1	34
> 150	34	3	3	0	40
Total	89	30	21	10	150

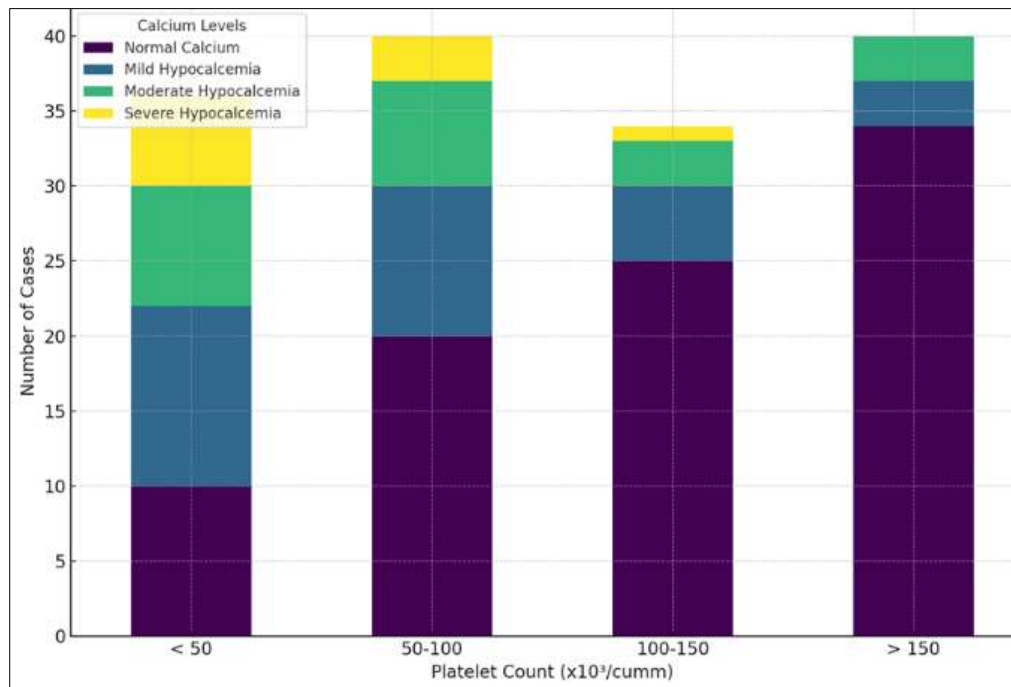


Fig 2: Distribution of hypocalcemia levels by platelet count

Here is the stacked bar chart visualizing the distribution of hypocalcemia levels by platelet count.

Table 8: Liver function tests by Calcium Levels

Liver Function Test	Normal Calcium	Mild Hypocalcemia	Moderate Hypocalcemia	Severe Hypocalcemia	Total
AST (U/L, Mean ±SD)	45±15	60±20	75±25	90±30	57±22
ALT (U/L, Mean ±SD)	40±14	55±18	70±22	85±28	52±20
Total Bilirubin (mg/dL)	0.9±0.3	1.2±0.4	1.4±0.5	1.6±0.6	1.1±0.4
Direct Bilirubin (mg/dL)	0.4±0.2	0.5±0.3	0.6±0.4	0.7±0.5	0.5±0.3
Total	89	30	21	10	150

Table 9: Renal function tests by Calcium Levels

Renal Function Test	Normal Calcium	Mild Hypocalcemia	Moderate Hypocalcemia	Severe Hypocalcemia	Total
Serum Creatinine (mg/dL)	1.0±0.2	1.2±0.3	1.4±0.4	1.6±0.5	1.2±0.3
BUN (mg/dL)	20±6	24±8	28±10	32±12	23±8
Total	89	30	21	10	150

Table 10: Clinical outcomes based on severity of hypocalcemia

Clinical Outcome	Normal Calcium	Mild Hypocalcemia	Moderate Hypocalcemia	Severe Hypocalcemia	Total
Resolution of Shock (Days)	2.5±0.5	3.0±0.7	4.0±0.9	5.0±1.0	3.0±0.8
Normalization of Platelet Count (Days)	3.5±0.6	4.0±0.8	5.0±1.0	6.0±1.2	4.2±0.9
Recovery from Transaminitis (Days)	4.0±0.7	4.5±0.9	5.5±1.1	6.5±1.3	4.7±1.0
Total	89	30	21	10	150

Discussion

The prevalence of hypocalcemia in dengue patients observed in this study was 40.7%, with 20% of patients experiencing mild hypocalcemia, 14% moderate hypocalcemia, and 6.7% severe hypocalcemia. This high prevalence aligns with previous studies indicating that hypocalcemia is a common

biochemical abnormality in dengue fever patients [11-14]. The significant presence of hypocalcemia underscores its importance as a clinical parameter to be routinely monitored in dengue patients to identify those at higher risk of severe outcomes.

Our findings reveal a significant correlation between

hypocalcemia and the severity of dengue fever. Patients with severe hypocalcemia showed a higher incidence of severe dengue forms, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Specifically, severe hypocalcemia was observed in 60% of DHF 1 & 2 cases and 20% of DSS cases (Table 3). This supports the hypothesis that hypocalcemia can be an indicator of disease severity, as suggested by other studies [15-17]. The decline in calcium levels with increasing severity of dengue highlights the potential role of calcium in maintaining vascular integrity and hemostasis, which are critical in managing severe dengue manifestations. Calcium supplementation had a notable positive impact on the clinical outcomes of patients with hypocalcemia. Among patients with mild hypocalcemia, those who received calcium supplementation had a reduced mean hospital stay of 3.13 days compared to 3.6 days for those who did not receive supplementation (Table 4). This indicates that calcium supplementation can significantly improve recovery times, potentially reducing healthcare costs and improving patient outcomes. Previous studies have also reported similar benefits of calcium supplementation in improving clinical recovery in dengue patients [19-25].

The duration to achieve normocalcemia varied with the severity of hypocalcemia, with mild cases achieving normocalcemia in 1.67 ± 0.994 days, moderate cases in 2.9 ± 0.7 days, and severe cases in 4.5 ± 0.527 days (Table 5). This progression suggests that early identification and management of hypocalcemia can expedite clinical recovery. Additionally, the duration to resolve shock also increased with the severity of hypocalcemia, further underscoring the importance of calcium in managing severe dengue cases. These findings align with those of Uddin *et al.*, who demonstrated that hypocalcemia is significantly correlated with the severity of dengue infection.

Clinical Implications

The clinical implications of this study are significant. The high prevalence of hypocalcemia and its correlation with disease severity suggest that routine monitoring of calcium levels should be integrated into the management protocols for dengue fever. Early identification of hypocalcemia can help in stratifying patients based on their risk of developing severe disease, allowing for timely and targeted interventions such as calcium supplementation. This could potentially reduce the morbidity and mortality associated with severe dengue.

Limitations

This study has some limitations. The sample size, while adequate, could be expanded in future research to confirm these findings across larger and more diverse populations. Additionally, the observational nature of the study means that while correlations can be drawn, causation cannot be definitively established. Randomized controlled trials are necessary to conclusively determine the efficacy of calcium supplementation in improving clinical outcomes in dengue patients.

Future Directions

Future research should focus on larger, multi-center studies to validate these findings and explore the mechanisms behind hypocalcemia in dengue fever more deeply. Investigating the role of other electrolytes and their interactions with calcium in the context of dengue could also provide valuable insights.

Moreover, exploring the timing and dosage of calcium supplementation in clinical trials could help establish standardized treatment protocols.

Conclusion

In conclusion, this study underscores the significant prevalence of hypocalcemia in dengue patients and its strong correlation with disease severity. The beneficial effects of calcium supplementation on clinical outcomes highlight its potential as a therapeutic intervention in dengue management. Routine monitoring and early intervention for hypocalcemia could enhance patient care, reduce morbidity, and improve recovery times, ultimately contributing to better health outcomes in dengue-endemic regions. Further studies with larger sample sizes and randomized controlled trials are needed to firmly establish these findings and guide clinical practice.

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