Severe Thrombocytopenia Associated with Dengue Fever and its Management by Using Platelet Concentrates: A systematic review

ABSTRACT

Dengue virus is a flavivirus, transmitted by mosquitos (Aedes aegypti). It represents an important global health problem, particularly in Brazil, India, Indonesia, Thailand, and the Philippines (countries in the tropics and subtropics). Dengue illness ranges from asymptomatic infection to severe dengue, characterized by plasma leakage or severe bleeding or organ impairment. Thrombocytopenia is fairly recognizable and potentially life-threatening in severe cases of dengue. This review aims to assess the efficacy of platelet concentrates in the treatment of severe thrombocytopenia associated with dengue infection. The study examines several literature articles according to the manner of data collecting. The information acquired was based on the analysis's objectives. Data analysis was done with articles, PubMed, google scholar and science direct. The relationship between Dengue infection and thrombocytopenia demonstrates the intricacies of dengue etiology and stresses the importance of targeted treatment strategies. This study investigated many pathways implicated in dengue-induced platelet decrease, including direct platelet infection, megakaryocyte suppression, and immune-mediated clearance. The findings indicate that medicines focused on these pathways have the potential to minimize the severe clinical effects of dengue.Furthermore, platelet concentrators have shown promise in the treatment of thrombocytopenia, offering a viable alternative for reducing bleeding risks and improving patient outcomes. Continued research into the molecular links between DENV and platelet biology is crucial for developing more effective treatments and, ultimately, improving clinical dengue fever care.

Keywords: Dengue fever; Thrombocytopenia; Platelet transfusion; Platelet concentrates

INTRODUCTION

One prevalent tropical infection is dengue fever. When this acute fever sickness manifests severely, it might be fatal and cause dengue hemorrhagic shock. I will provide an overview and talk about this disease's diagnosis and therapy in this short post. Most tropical physicians employ presumptive diagnosis when diagnosing dengue; nevertheless, an immunodiagnostic or viral study should be the basis for a definitive diagnosis. The primary therapeutic approach focuses on treatment, including supportive and symptomatic care. Although it hasn't been extensively researched, antiviral medications have a limited role in the management of dengue fever [1].

Dengue fever, the most rapidly expanding vector-borne disease in the world, has risen markedly during the twenty-first century[2]. His is an illness caused by dengue virus (DENV), which is mainly transmitted by Aedes aegypti mosquito [3]. DENV infection can occur in different patterns, ranging from mild febrile illness to severe dengue characterized by capillary leakage, hemorrhage and organ failure[4].Severe dengue also involves thrombocytopenia, a condition defined as abnormally low blood platelet levels that can worsen bleeding and complicate clinical management of this disease[5]

One of the most prominent clinical symptoms of dengue virus infection is a decrease in white blood cells and platelets in human peripheral blood (leukopenia and thrombocytopenia, respectively), which can greatly hamper dengue virus clearance by the immune system. The etiology of thrombocytopenia and leukopenia during dengue infection is unknown, however it could be due to severe suppression of bone marrow populations such as hematopoietic stem cells and megakaryocytes, which are the progenitors of white blood cells and platelets, respectively.[6]

Platelet concentrate infusions are required for the treatment of central thrombocytopenia caused by a variety of factors, and this therapy is especially beneficial in those who are at risk of major

bleeding.[7].The grounds for platelet transfusion in dengue fever are clearly defined in World Health Organization (WHO) guidelines-2011, but doctors face practical challenges in executing them in an epidemic setting.[8]

1.AIM AND OBJECTIVE

1. To evaluate the effectiveness of platelet concentrates in the management of severe thrombocytopenia associated with dengue fever.
2. To assess the prevalence and severity of thrombocytopenia in patients with dengue fever.
3. To assess clinical outcomes associated with severe thrombocytopenia in dengue fever patients.
4. To elucidate the mechanisms through which dengue virus (DENV) infection induces thrombocytopenia

2. METHODOLOGY

The study reviews various literature article by method of data collection. information gathered based on the objectives of the analysis. All the data were collected through various journal, magazine, research paper and publications. The site followed was google scholar, pub med and science direct.

3. REVIEW

3.1 Review analysis on the effectiveness of platelet concentrates in the management of severe thrombocytopenia associated with dengue fever

Recent evidence has largely addressed their relationships to severe dengue and associated problems of blood management. Sondo et al. determined a variety of risk variables for serious dengue, regarding accurate details including age and men sex together with medical ailments which include hemoglobin S, diabetes mellitus as well as symptoms of asthma hypertension combined main illness. Altogether, the results indicate a combination of factors at play that contribute to why some people only develop mild disease.[9]

Complementing this, Ansari et al. (2023) noted the critical role of blood component in managing severe dengue cases, when patients experience severe thrombocytopenia. This highlights the necessity of prompt and proper blood product administration in dengue therapy.[10]

Further supporting this, de Sousa Oliveira et al. (2023) reported a strong association between increased dengue cases and mortality rates and the requirement for certain blood products like platelet concentrates, fresh frozen plasma and cryoprecipitate during an outbreak of dengue.This not only emphasizes the importance of blood product utilization in dengue but also the potential pressure on blood banks during epidemics.[11]

The results of an observational study by Isharat, S et al showed that dengue fever can be treated symptomatically in accordance with WHO standards, and platelet transfusion is only necessary in cases of bleeding diathesis or when the platelet count is less than 10,000/cumm [12].

Dogra, A., et al investigated 20 patients were diagnosed as dengue confirmed cases using serological testing methods. Out of 20 patients, 12 (60%) had dengue fever, with platelet counts ranging from 50,000 to 80,000/µl. Two Dengue fever patients with Petechial spots and platelet counts ranging from 50,000/µl received preventive Single Donor Platelet Transfusions. Eight patients (40%) had Dengue hemorrhagic fever and a platelet count of less than 20,000/µl. These patients received single donor platelet transfusions. Six patients responded positively, with CCI levels exceeding 30,000/µl, whereas two patients did not respond.[13]

The results of the study by Tewari, K., et al, there were 57 youngsters ranging in age from 6 months to 77 years old and 443 adults. 115 individuals, or 23%, had positive NS1 results. Severe bodily aches (97.4%) and fever (99.8%) were the most frequent presentations. 429 instances (85.6%) had DF, 55 cases (11.1%) had DFWS, 10 cases (2%) had SD with severe bleeding, and 6 cases (1.2%) had SD with severe plasma leakage. In 412 cases (82%), OPD care was required, and in 88 cases (18%), hospitalization was required. In 16 (3.2%) of the patients, intravenous fluid resuscitation was required. At presentation, 335 individuals (67%) had thrombocytopenia. In 46 cases (9.2%), a platelet transfusion was required. Ten patients with significant bleeding from SD and three patients with DFWS received packed red blood cell (PRBC) transfusions. Three SD patients with significant plasma leaks and two SD patients with serious bleedings died.[14]

The results of the study by Hassan, J., Borhany, M et al, 200 patients were chosen, with a mean age of 28.68 years (±13.28) and a preponderance of males (147/200). Mean platelet count, hemoglobin, and hematocrit at baseline for bleeding and non-bleeding individuals yielded significant results; bleeding individuals had a platelet count of 24,000 at baseline, while non-bleeding individuals had a platelet count of 29,000, which demonstrated a significant link with bleeding (P-value =.027). 76 patients (38%) received platelets by transfusion.[15]

When bleeding from thrombocytopenia complicates a dengue episode, platelet transfusions are frequently given. Whether this technique leads to an increase in clot strength is unclear, though. In this study by Sundar, V., & Bhaskar, E., 74 dengue patients' levels of bleeding control and improved clot strength as determined by thromboelastography were evaluated in relation to platelet transfusion. The impact of one unit of single donor aphaeresis units or weight-based random donor platelets was investigated. A mean platelet count increase of 10,210 cells per mm3 from pretransfusion values was seen 24 hours after transfusion of weight-based random donor platelets. This rise approached borderline statistical significance ($p = 0.031$).At 24 hours, the mean platelet augmentation of patients receiving single donor platelets was 22,874 cells per mm3, with a significant statistical significance ($p < 0.001$). However, in thromboelastography, there was no discernible increase in clot strength. In the random donor platelet group, the mean increment in the maximum amplitude value at 24 hours was only 2 mm, whereas in the single donor group, it was 5 mm. Neither of these increments reached statistical significance. In addition, most of the patients continued to hemorrhage even after receiving platelets. This study found that while the absolute platelet counts increased following platelet transfusion, the clot strength did not improve in dengue patients experiencing bleeding complications.[16]

The results of the study by Nasir, A et al the average age of the 107 patients was 53 years (±19.05), with 44 (41.1%) female and 63 (58.9%) male. Platelets were requested for 93 patients (86.7%), platelets and fresh frozen plasma for 3 patients (2.8%), platelets and whole blood for 9 patients (84.4%), and whole blood for 2 patients (1.9%). 35 patients (32.7%) had therapeutic platelet transfusions, while 72 patients (67.3%) received prophylactic platelet transfusions.[17]

Kansay, S., et al concluded that 25,703/cumm was the average platelet count at which platelet transfusion was started. The average quantity of random donor platelets (RDPs) transfused fell dramatically in 2015 (5.4 vs. 4.3 in 2013) as a result of SDAP transfusions to patients with high-risk variables overlaid on their platelet counts and extremely low platelets. The average duration of hospitalization was comparable for patients on RDP alone and for those on RDP and SDAP combined (5.48 vs. 5.54), but it was much shorter (3.6) for patients on SDAP alone.[18]

Machado, A. A studied 323 patients, 52 underwent transfusion, with 52% of them lacking criterion ($n = 27$), while 271 did not receive transfusion, with 4.4% ($n = 12$) having criteria. The mean duration of hospitalization was greater for patients who did not receive a transfusion.[19]

Buddharaju, C. D. V. B., et al observed that at 24 hours post-transfusion, SDP transfusions resulted in significantly higher platelet increases compared to RDP transfusions ($p<0.01$). However, both groups' corrected count increment and % recovery was practically identical, and the difference was statistically insignificant.[20]

The results of the study by Asha, J, there were 250 samples in all. In dengue patients, the investigation revealed normal PDW and MPV, low platelet counts and PCT, and elevated PLCR and IPF. Based on platelet transfusion, there were statistically significant changes in PIs (greater MPV, PDW, PLCR, and IPF, lower platelet count and PCT).[21]

It was observed by Archuleta, S., Chia, P. Y et al 158 out of 360 patients had inadequate platelet recovery. Once baseline features and platelet transfusion were taken into account, age, white cell count, and day of illness at study entry were found to be significant predictors of poor platelet recovery. Regardless of transfusion, patients with poor platelet recovery were in hospitals for longer periods of time, but there was no discernible difference in other clinical outcomes. Patients with poor platelet recovery were more likely to hemorrhage if given a prophylactic platelet transfusion (odds ratio 2.34, 95% confidence interval 1.18-4.63). They detected a significant interaction between platelet recovery and transfusion.[22]

A study by Sethi, S. M et al, out of the total dengue patients, 32.7% received platelets through transfusion (group 1), whereas 67.3% did not (group 2). Minor bleeding episodes differed significantly between the transfused group and the non-transfused group (65(31.1%) vs. 59(13.7%); p=0.000). In a similar vein, 1(0.2%) versus 4(1.9%) patients in group 2 (p=0.024) died.[23]

A study by Rao, C. A et al, 100 out of 200 patients received FFP transfusion alone, resulting in a substantial increase in platelets (p-value < 0.001), while 26 patients had SDP transfusion alone, resulting in a mean increase in platelets (p-value = 0.023). Out of 200 patients, 74 received FFP followed by SDP, resulting in a mean platelet increase with a p value of <0.001. The mean length of hospital stay with FFP followed by SDP shows a significant p-value.[24]

3.2 Review analysis on the prevalence and severity of thrombocytopenia in patients with dengue fever.

Chowdhury et al. investigated on dengue fever in Bangladesh with respect to the outbreak of 2022 that reported the highest dengue vaccine mortality rate (281). Regarding the febrile phase (≤ 4 days), the study also identified following factors as likely to be severe disease indicators including thrombocytopenia, hemoconcentration, hypotension. The study indicates that these factors might be predictors of the disease moving to the next level of severe dengue.[25]

Dengue infections in children were examined in the work of Pathak et al., where viral load was investigated in association with clinical aspect. What they demonstrated is that while high viral load expressed as copies/ ml was greater than 106, showed a direct relation with the hematocrit concentration, it was inversely related to the platelet count. Based on the study, the viral load could be another significant factor in the prognosis of severe clinical manifestations such as thrombocytopenia and elevated hematocrit in the infection with dengue virus.[26]

Castilho, B. M., et alconducted a retrospective cohort study to determining the factors responsible for increasing risk of thrombocytopenia in dengue patients. They collected data from 387 Brazilian patients, of whom 156 developed thrombocytopenia. There were three independent identified key risk factors such as male sex, older age below or equal to 46 years, leukopenia and high mean corpuscular hemoglobin levels. These host factors which could render dengue patients more susceptible for developing thrombocytopenia that may increase their risk of haemorrhagic complications with infection [27].

Tayal, A., et al noted severe dengue is characterized by plasma leakage, severe bleeding, or organ dysfunction. Dengue has no known cure; supportive care is the only available treatment. The cornerstone of dengue management during its critical phase is prudent fluid resuscitation.[28]

Shah, D., et all found thatcommon tropical viral diseases like dengue frequently result in thrombocytopenia, which can cause bleeding and necessitate blood transfusions. Platelet count and immature platelet fraction were found to be strongly correlated in our study of 124 dengue patients. They also found that 96.1% and 97.4% of patients, respectively, had an increase in platelet count at 24 and 48

hours. In 64% of patients with an IPF level of 10% or above, platelet transfusion was avoided in the absence of bleeding.[29]

Study by Quirino-Teixeiranoted that thrombocytopenia is a crucial feature of DENV infection that can be seen in both moderate and severe cases, while severe patients have the lowest platelet counts. They compile data on various pathways linked to changes in platelet quantity and function, which can result in thrombocytopenia as well as platelet-mediated immunological and inflammatory responses.[30]

A study by Looi, K. W et al suggest that during the first week of sickness, all patients experienced a declining trend in platelet count, which was accompanied by an increasing trend in the percentage of immature platelets to total platelets (IPF%) for more than three days before platelet recovery. On days 3–5 following the beginning of fever, patients with severe dengue exhibited a significantly higher IPF% in comparison to those with non-severe dengue.[31]

By the study of Tulara, N. K, it was observed that, upon admission, 97% of the patients with serologically confirmed positive cases had thrombocytopenia (count <100,000/mm3), and no patient had bleeding issues.[32]

A systematic review by Rajapakse, S et al, observed, between 1990 and 2013, the incidence of dengue fever increased seven times worldwide. During epidemics, total mortality rates can be considerable despite a low case fatality rate (<1%) because of the large number of affected individuals. In dengue, there is an unknown chance of clinically substantial bleeding, which frequently leads to a negative outcome [33]

Khatri, S et al concluded that in dengue fever cases with thrombocytopenia, the platelet histograms (MPV, PDW, and Plateletcrit) produced by the Beckman Coulter counter LH755TM and LH780TM series were evaluated. It was found that the mean platelet volume (MPV) was 9.01 fL (SD = 0.09). The median plateletcrit was 0.47 (IQR 0.2–0.8) and the mean platelet distribution width was 17.2% (SD = 0.98). No one who took part in the trial experienced bleeding symptoms. No appreciable alterations in platelet parameters were found in dengue cases with thrombocytopenia in the current investigation.[34]

A study by Brahma, Aet al showed that the mean MPV was substantially lower (p value < 0.0001) on the day before, when the platelet count was less than 20,000/cu.mm, in comparison to the mean MPVs of all patients.[35]

Zeb, S., Qaisar, Oet al noted that out of the total suspected cases, people tested positive, with men making up the majority (65.3%) compared to women (34.7%). White blood cells, platelets, and hemoglobin levels were the lowest at 6.9 g/dl, 2400 g/dl, and 43000 g/dl, respectively. 9.4% of patients had low hemoglobin levels, 25.3% had white blood cell counts that were below normal, and 30.4% had platelet counts that were below normal. Fewer patients than usual were found to have lower mean platelet volumes and platelet crits.[36]

3.3 Review analysis on clinical outcomes associated with severe thrombocytopenia in dengue fever patients.

Shabir, M., et al concluded that there is a positive correlation between platelet count and bleeding complications in dengue patients; however, certain types of bleeding, such as melena, hematemesis, hemoptysis, and per vaginal bleeding, are not directly associated to blood platelet counts.[37]

Patel, K. B., Ranapurwala et al noted that dengue cases commonly present with fever 32.65% or fever with chills / rigidity 66.33%, headache 37.76%, body aching 44.90%, and bleeding symptoms such as petechiae 5.10% and bleeding from the gums, nose, and rectum 5.15%. In dengue-positive cases, 18% had ascites, and 7% have pleural effusion. The severity of dengue infection is significantly associated with hemoconcentration, a decrease in total WBC count, platelet count, and plateletcrit. Platelet count was directly linked to plateletcrit in dengue-positive cases.[38]

Patel, G. Ret al concluded that coagulation problems were found in 42.8% of the patients. Overall, the most prevalent coagulation abnormality was extended aPTT (40.8%), followed by low fibrinogen (38.7%), high D-dimer (31.2%), elevated INR (26.0%), and prolonged PT (19.2%). 19.9% of patients showed signs of bleeding. Patients with bleeding had significantly greater levels of PT, INR, aPTT, and D-dimer ($P<0.01$) and lower levels of fibrinogen ($P<0.001$) than those without bleeding. Patients with bleeding reported significantly greater rates of coagulation anomalies compared to those without bleeding ($P<0.01$).[39]

Irshad, Z., et al concluded that while platelet count can be a predictor of disease and how it will proceed, it cannot be used to rule out disease progression. Dengue fever remains a serious health concern in Pakistan.[40]

Archuleta, S., et al. concluded that dengue patients with thrombocytopenia who were older or presented sooner, as well as those with lower white cell counts, were more likely to experience poor platelet recovery. Platelet transfusions may not enhance outcomes in individuals with poor platelet recovery and may even increase the risk of bleeding. The mechanisms of inadequate platelet recovery must be established.[41]

3.4 Review analysis on mechanisms through which dengue virus (DENV) infection induces thrombocytopenia

Losada, P. X., et al observed that the dengue virus infects and activates platelets, allowing them to be eliminated by phagocytic cell identification and peripheral marginalization. Infection, however, has an effect on bone marrow precursors via modifying megakaryopoiesis; it results in thrombocytopenia. [42]

Fang et al. examined the contribution of platelets in virusinfections. Through another exciting research, they concluded that platelets can store and release SFTSV particles. Platelet aggregation is caused by the viruses' propensity to adhere to platelet glycoprotein VI and then promote platelet activation. In terms of the specific interactions between platelets and macrophages, the platelet-macrophage interactions are beneficial for SFTSV clearance but at the same time, this interaction can stimulate unwanted replication of SFTSV within macrophages, which can play a role in thrombocytopenia and various other clinical manifestations.[43]

In review of Singh, A., et all., nucleated blood cells called platelets are produced from bone marrow megakaryocytes and are essential for thrombosis and hemostasis. Platelets are made up of specialized storage organelles termed alpha-granules, which are rich in cytokines such as transforming growth factor β (TGF-β), CXCL (also known as interleukin 8; IL-8), and C-X-C motif ligand (CXCL) 1/4/7. Platelets that have been activated degranulate and release their contents into the plasma. Numerous viral diseases, such as the human immunodeficiency virus (HIV), the H1N1 influenza, the hepatitis C virus (HCV), the Ebola virus (EBV), and the dengue virus (DENV), frequently cause platelet activation, when platelets are activated, they release substances called fibrinopeptides, CCL5, and CXCL4 (sometimes referred to as platelet factor, PF4), which are vital regulators of the host's ability for multiple viruses to replicate and spread.[44]

García-Larragoiti, N.,et al studied platelet surfaces, the DENV NS1 protein and its domains stimulate the production of P-selectin and the αIIbβ3 complex. When a small amount of collagen, epinephrine (EPI), or adenosine diphosphate (ADP) is added, DENV NS1 causes a stable platelet aggregation. Interestingly, upon incubation with the NS1 protein domains, only EPI was able to cause the development of platelet aggregates.[45]

Yang et al are concern with the Prothymosin α (ProT) in dengue virus (DENV) thrombocytopenia. In their study increased amounts of ProT in the sera of dengue patients and in megakaryoblasts infected with DENV. They outline a signaling cascade, which includes miR-126, DNMT1, GATA-1, ProT, and Nrf2 in thrombocytopenia caused by DENV. They also noted decreased platelet count in the ProT transgenic mice and they also noted that ProT overexpression inhibited megakaryocyte differentiation [46]

Masri et al. also argue that thrombocytopenia mechanism in dengue virus is different and new by proposing that serotonin from mast cells play a critical role. They showed that during dengue virus infection, MCs release serpentine, which triggers the platelets activating the aggregation and phagocytosis through 5HT2A receptors. This study proves that MC deficiency or usage of chemicals to inactivate MCs eliminated thrombocytopenia in mice.[47]

The monitoring of platelet counts and immature platelet fraction (IPF) has been shown to be useful in the prediction of both subsequent recovery from thrombocytopenia as well as progression towards disease. Dudnyk, V. M., et al. concluded that viral infections cause platelets to be activated and produce immune response. Also, they noted that the presence of antiplatelet antibodies results thrombocytopenia. They states the mechanism of inducing thrombocytopenia in that these antibodies attach themselves to particular glycoproteins found on the surface of platelets that triggers both phagocytosis and subsequent death of platelets themselves.[48]

Chao et al. conducted a studyto recognized the involvement of dengue virus nonstructural protein 1 (DENV NS1) in platelet activation and thrombocytopenia during dengue infection. This research clearly supports the involvement of DENV NS1 in platelet activation, leading to platelet reduction and hemorrhage in dengue[49].

Banerjee et al. observed noted a relation between the virus envelope protein and an important transcription factor for megakaryopoiesis (TAL-1).[50]

CONCLUSION

Thrombocytopenia is a common clinical symptom of dengue viral fever and many studies were conducted with the aim to detectingindictors possible for early diagnosis and treatment in severe cases. The rapid decrease of platelet count is due to platelet activation, suppression of bone marrow and interaction with megakaryocytes. These mechanisms need to be study thoroughly for developing effective therapies that can mitigate thrombocytopenia in dengue affected individuals. Low platelet counts in dengue patients associated with severe clinical complications such as an increased bleeding tendency due to thrombocytopenia. Results will only get better with a diversified approach to monitoring and management.These findings suggest that the efficacy of platelet transfusions is varied, but it represents a common therapeutic management for severe thrombocytopenia in dengue virus infection and additional study should be conducted to better define the parameters whereby they may or may not clearly benefit these patients.

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3. Claude.AI 3.5 sonnet for summaries some article only, prompt- write summary for this abstract, after that written in myown words.

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