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DENGUE AND PLATELET TRANSFUSION: ASSESSING THE APPROPRIATENESS AND CLINICAL OUTCOMES

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Abstract

Introduction

Dengue was caused by Dengue virus, an arboviral infection (Kurukularatne et al. 2011) seen worldwide, especially along the tropical and subtropical countries (Gupta et al. 2012). By bite of female Aedes aegypti mosquitoes is transmitted among humans (Whitehorn and Farrar 2010). Dengue virus, referred to Flaviviridae family, and comprises 4 different serotypes: DV-1, DV-2, DV-3, DV-4(Liker et al. 2022). Dengue is endemic in approximately hundred countries globally(Hill-Strathy et al. 2021). Incidence of Dengue was increasing globally (Thrombocytopenia and Platelet Transfusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome, n.d.), with Southeast Asian countries, which include India, Indonesia, Thailand, and Myanmar, accounting for the majority of global incidence. Population growth, urbanization, and inadequate water management contribute to mosquito proliferation (Shivbalan et al. 2004). As per the "National Vector Borne Disease Control Program" of India, case detection and vector control remain important strategies for prevention as well as spread of virus (Kurukularatne et al. 2011).

INTRODUCTION

Dengue is caused by Dengue virus, an arboviral infection (Kurukularatne et al. 2011)seen worldwide, especially along the tropical and subtropical countries (Gupta et al. 2012). Bite of female Aedes aegypti mosquitoes is transmitted to humans (Whitehorn and Farrar 2010). Dengue virus is a member of Flaviviridae family and consists of 4 different serotypes: DV-1, DV-2, DV-3, and DV-4..(Dayarathna et al. 2024) Dengue virus is found to be endemic in around 100 countries worldwide (Hill-Strathy et al. 2021). Incidence of Dengue was increasing globally "(Thrombocytopenia and Platelet Transfusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome, n.d.)", with Southeast Asian countries, which include India, Indonesia, Thailand, and Myanmar, accounting for the majority of global incidence. Urbanization, population growth, and inadequate water management contribute to mosquito proliferation (Shivbalan et al. 2004). Per India's "National Vector Borne Disease Control Program" of India, case detection, management and vector control remain important strategies for preventing and spreading the virus (Kurukularatne et al. 2011).

Dengue infection manifests a range of clinical symptoms, ranging from mild, similar to influenza, to severe dengue illness (Shivbalan et al. 2004). The standard clinical manifestation of Dengue fever is an abrupt onset of fever accompanied by retro-orbital pain. arthralgia, myalgia, vomiting, as well as a generalized weakness (Hill-Strathy et al. 2021). The maculopapular rash, which is generalized and appears a day or two after fever, occurs during recovery phase (Hill-Strathy et al., 2021). As per WHO, Dengue is classified as the following: (DHF) Dengue hemorrhagic fever, (DF) Dengue fever, as well as (DSS) Dengue shock syndrome. Dengue fever is characterized

by an acute febrile illness accompanied by myalgia, headache, retroorbital pain, arthralgia, as well as rash "(*Thrombocytopenia and Platelet Transfusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome*, n.d.)". DHF is defined as fever, thrombocytopenia, and bleeding manifestations "(*Thrombocytopenia and Platelet Transfusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome*, n.d.)". Bleeding manifestations usually range from petechiae, purpura ecchymosis, gum bleeds, vaginal bleeding, as well as evidence of plasma leakage [hematocrit > 20%/presence of pleural/abdominal effusion/hypoalbuminia]. Dengue shock syndrome is distinguished by rapid, weak pulse as well as reduced pulse pressure. "(*Thrombocytopenia and Platelet Transfusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome*, n.d.)". Dengue fever is a self-limiting illness, along with most patients recover without complications, generally within 10 days of symptom onset. This may be associated with minor hemorrhagic symptoms like petechiae (Hill-Strathy et al. 2021). Nonetheless, some patients may advance to DMF and DSS, serious forms of dengue fever. In severe cases, increased vascular permeability and plasma leak are observed. Spontaneous bleeding is typically linked to severe symptoms of Dengue fever. (Hill-Strathy et al., 2021). Dengue patients exhibit elevated levels of cytokines, C3a and C5a [chemotactic complement anaphylatoxins], and histamines, all promoting vascular permeability. Endothelium also plays an important role in immune-mediated pathology, leading to increased vascular permeability in DHF and DSS (Hill-Strathy et al. 2021).

Thrombocytopenia is the most prominent feature of dengue infection, which is due to immunological destruction, resulting in altered haemostasis in the patients "(*Thrombocytopenia and Platelet Transfusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome*)". Thrombocytopenia and mild hepatic derangement are thought to act synergistically, resulting in varying bleeding manifestations (Gupta et al. 2012). Patients experiencing bleeding signs or hemorrhagic symptoms require platelet transfusion support since severe bleeding is directly linked to severe thrombocytopenia ("Technical Manual, 21st Edition - Print,").

MATERIALS & METHODS

Study Design

Present paper constitutes a retrospective study conducted at our blood center.

Setting

Research was performed at Saveetha Medical College and Research Center, Department of Transfusion Medicine and Immunohematology, for one year, from 1 January 2023, to 31 December 2023.

Participants

99 patients diagnosed with Dengue required platelet transfusion support during the above study period. The diagnosis of Dengue was based on clinical suspicion followed by serological confirmation. Laboratory confirmation was by NS1 [Non-structural protein 1] positivity or by confirmation of anti-dengue IgM and IgG antibodies (DGHS).

Inclusion and Exclusion criteria

Only Dengue positive [NS1 positive or Dengue IgM positive] patients for whom the platelet transfusion request was sent to our blood center were taken into the study. Patients with thrombocytopenia due to other causes, as well as Dengue-positive individuals who didn't require platelet transfusions, had been excluded from the study. Patients' clinical information and laboratory investigation results were obtained from the digital records of our institution, platelet requisition forms, cross-match registers, and issue registers within our Blood center.

Statistical methods

Collected data has been analyzed according to several platelets issued to each patient, the therapeutic indications or rationale for the platelet requests, the platelet count, relevant patient symptoms, and patient post-platelet transfusion status.

Appropriateness was categorized as per the WHO [World Health Organization] bleeding score Table *1* and DGHS "[Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India]" criteria Table *2*. and Table *3*.

Platelet transfusion indications are either therapeutic or prophylactic; Therapeutic platelet transfusions are administered to address active bleeding, whereas prophylactic platelet transfusions are conducted to avert any bleeding occurrences. Prophylactic platelet transfusions are given to individuals with a WHO bleeding score of equal to <1. Therapeutic transfusions are administered when WHO bleeding score is equal to >2. (Simon et al. 2016).

Table 1 WHO Bleeding Score (*DGHS TRANSFUSION MEDICINE TECHNICAL MANUAL)

Grade of bleeding	Type of bleeding
1	• "Petechiae or purpura—localized type, at one or two dependent sites which are sparse/non-confluent • Oropharyngeal bleeding or epistaxis" that lasts for less than 30min minutes
2	• Hematemesis, melaena, musculoskeletal bleeding, fresh blood in stool, hemoptysis, or soft tissue bleeding that doesn't necessitate an RBC transfusion within 24 hrs of onset, as well as does not exhibit any signs of hemodynamic instability. • Oropharyngeal bleeding or Profuse epistaxis of more than 30min • Symptomatic oral bleeding or the one that causes major discomfort • Multiple bruises, each more than 2 cm or anyone more than 10 cm •Diffuse type of Petechiae or purpura • Haematuria (macroscopically visible) • Any instance of "abnormal bleeding from invasive or procedural sites • Unexpected vaginal bleeding which saturates >2 pads within a" 24hrs duration • "Bleeding in cavity fluids with microscopical evidence • Retinal hemorrhage absent visual impairment
3	• Bleeding necessitating RBC transfusion support during 24hrs of onset, without hemodynamic instability. • Grossly visible Bleeding in body cavity fluids • Cerebral bleeding, identified on computed tomography (CT) without accompanying neurological signs or symptoms".

4	• Any type of encompassing retinal bleeding, debilitating bleeding, as well as "visual impairment. • Cerebral bleeding with neurological signs as well as symptoms (non-fatal) • Bleeding accompanied by hemodynamic instability (hypotension with a change exceeding 30 mmHg in systolic or diastolic blood pressure) • Life-threatening bleeding from any" place

Table 2: Indication for Prophylactic platelets transfusion (reversible or chronic bone marrow failure resulting in thrombocytopenia) (*DGHS-TRANSFUSION MEDICINE TECHNICAL MANUAL)

Indication	Transfuse platelet at
WHO score 0 or 1: no clinically significant bleeding, no invasive procedure planned, and on intensive chemotherapy or undergoing allogeneic HSCT	< 10,000/ µl
Bone marrow aspirate/trephine biopsy/cataract surgery	< 10,000/µl
As above but with additional risk factors for bleeding, e.g., venous central lines (tunneled/untunneled)	<20,000/µl
Lumbar puncture	<40,000/µl
Insertion or taking out an epidural catheter	<80,000/µl
Major surgery or percutaneous liver biopsy or renal biopsy (provided anemia and uremia are corrected)	<50,000/µl
Neurosurgery/ophthalmic surgery, which involves posterior segment of the eye	<100,000/µl
WHO* bleeding score >2	No trigger; manage individually according to the symptoms

Table 3: Indication for therapeutic platelet transfusion (*DGHS-TRANSFUSION MEDICINE TECHNICAL MANUAL)

Indication	Transfuse platelet at
WHO bleeding score >2 and severe life-threatening bleeding	No trigger, manage individually according to the symptoms and maintain platelet count >50,000/ µl
Traumatic brain injury, Multiple trauma, or spontaneous intracerebral hemorrhage	Less than or equal to 100,000/µl

Nonsevere and/ or non-life-threatening bleed	Less than or equal to 30,000/µl

[*DGHS - Directorate General of Health Services: TRANSFUSION MEDICINE TECHNICAL MANUAL, Ministry of Health & Family Welfare, Government of India, India; 2022]

RESULTS

Participants

During the period of study, 99 patients who were diagnosed with dengue had been issued platelet transfusions. Only one of the 99 patients was under the pediatric department, the rest were under the general medicine department.

Outcome

For the above patients, in total 572 random donor platelets [RDPs] as well as 91 Single donor platelets [SDPs] had been issued. Only one transfusion episode was taken into count per patient in this study. One of the 99 patients participating in the survey succumbed during the hospital stay. Table 4 shows various bleeding manifestations and the respective range of the patient's platelet counts.

Table 4: Bleeding manifestations and the respective Platelet counts

Platelet count: thousands/cumm	**Bleeding Manifestations**	**<10**	**11-20**	**20-30**	**>30**	**Total**
No. of Patients with	Haematemesis	1	1			2
	Melena	10	5	1		16
	Gum Bleed	3	3			6
	Petechiae Rashes	2	2			4
	Menorrhagia	2				2
	IC Bleed		1			1
Total patients with bleeding manifestations		18	12	1		

Total No. of Dengue Patients who received Platelets transfusion (with and without proper indications)		**45**	**44**	**6**	**1**	**99**

Figure 1 Appropriate versus Inappropriate Platelet Transfusion

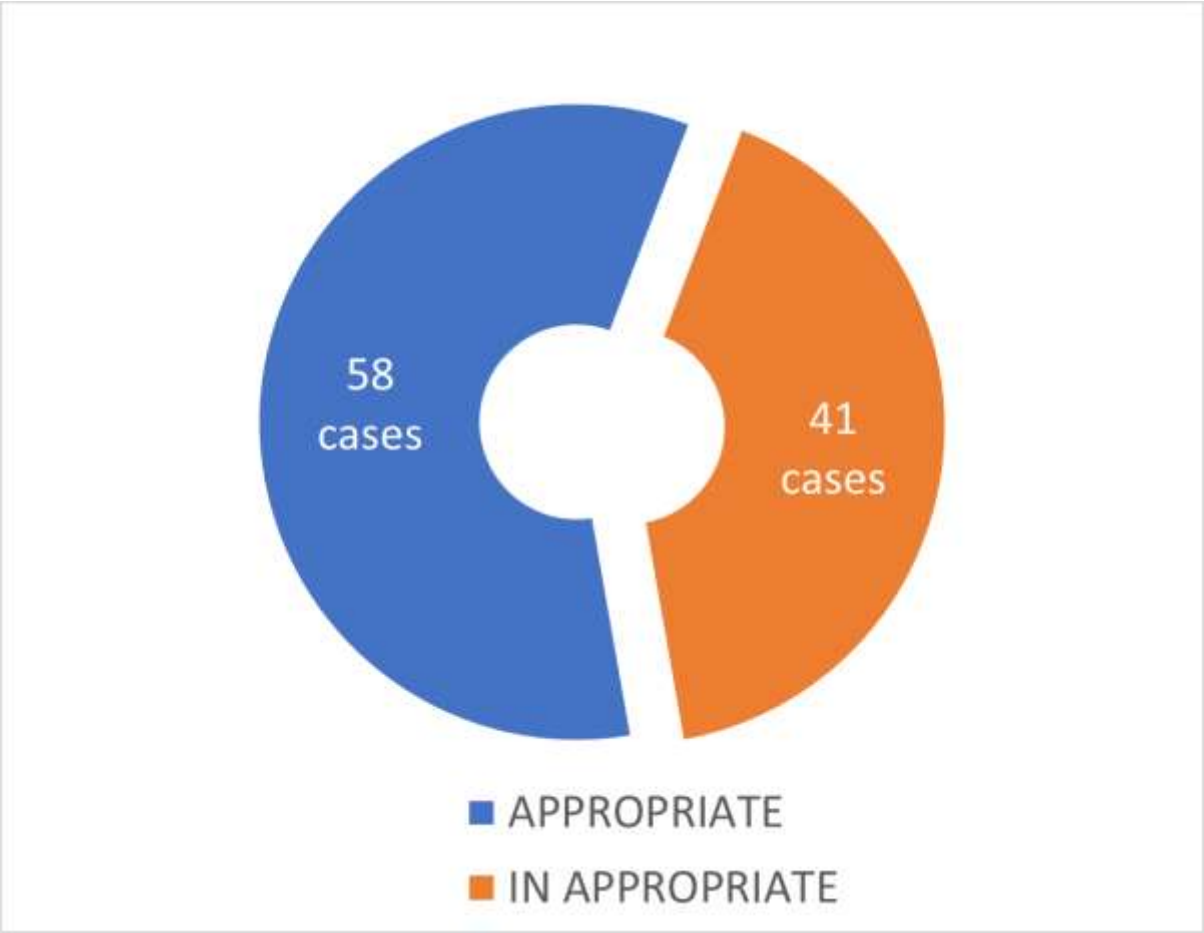
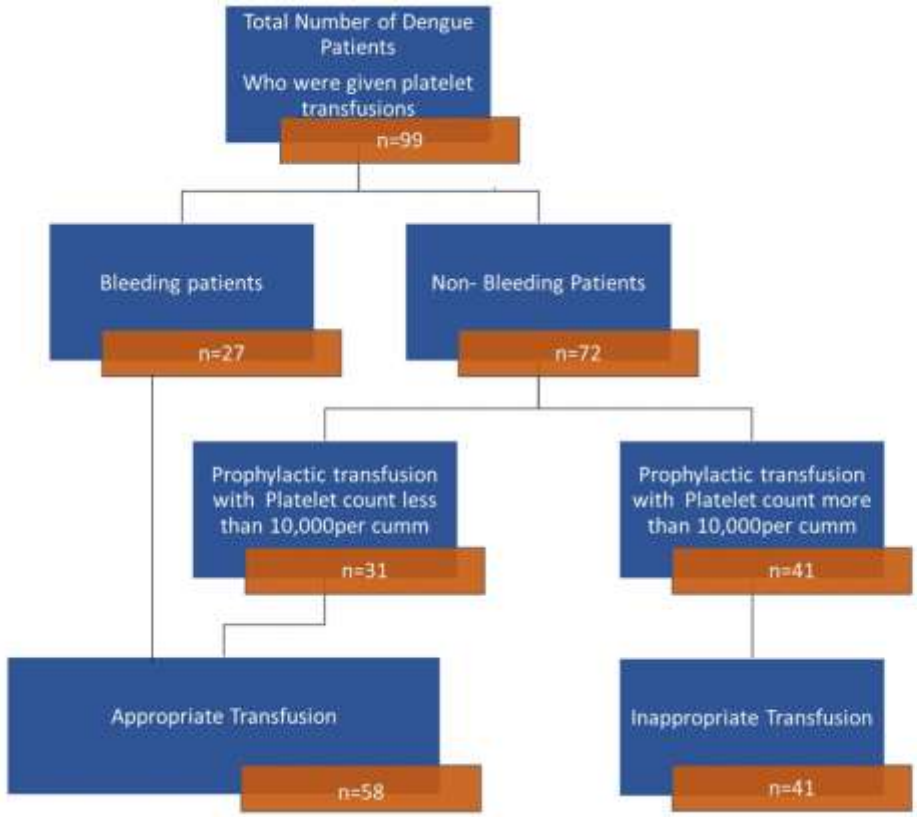


Figure 2 Dengue – Platelet usage



Our study found only 58 of the 99 platelet transfusions were appropriate. The remaining 41 were inappropriate (Figure 1). Figure 2 shows the platelet usage in the Dengue case. Among the above 99 cases that received transfusion support, only one mortality involved an intracranial bleed. All other cases showed clinical improvement.

DISCUSSION

The dengue virus is endemic to India, with most dengue-positive cases seen among the adult population. It is, at present, a major health problem in India. Most cases were seen among age groups of 21 to 30. This was also observed by Makroo et al. (Makroo et al. 2007). Bleeding is mostly seen in cases with platelet counts <20,000/cumm. Similar study results were observed by *Shivbalan et al.* (Shivbalan et al. 2004) while *Chairulfatah et al.* observed that most of the severe bleeding manifestations were when platelet counts had gone below 15,000/cumm (*Thrombocytopenia and Platelet Transfusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome*, [*DGHS - TRANSFUSION MEDICINE TECHNICAL MANUAL)

Of the 99 patients in our study who underwent platelet transfusions, 41 had received the transfusions without the proper indications. This data has been represented in Figure 1. This finding is almost similar to the finding by Ahamed et al., which found around 56% of inappropriate platelet transfusions for patients diagnosed with dengue (Hill-Strathy et al. 2021).

Dengue patients are mostly admitted to hospitals to manage bleeding manifestations and thrombocytopenia. Most of the public fears of the diseases are responsible for inappropriate platelet transfusions. In most cases, there are no real medical indications for platelet transfusions. The clinical physicians treating the patients are usually under

social pressure from both patients and their respective relatives and, hence, are forced to transfuse platelets. Especially during seasons of high Dengue cases, there is a panic response to the disease, and due to increased anxiety from the patients and their relatives, this contributes to inappropriate platelet transfusions. Most of these inappropriate platelet transfusions occur during the Dengue epidemics. Hence, during such outbreaks, there is a rise in platelet demand. Patients and the treating physicians have a tendency to chase the platelet counts, thus resulting in platelet transfusions to patients who were otherwise asymptomatic (Whitehorn and Farrar 2010). Platelet transfusion can be avoided in stable dengue patients with no risk of bleeding unless the counts go below, as advised by the guidelines. Increasing the platelet counts with platelet transfusions has shown no protective effect benefits in the patients (Muralidhar, Poojari, and Bilal 2021).

The primary cause of improper platelet transfusions is insufficient awareness of the adverse effects and risks linked to the transfusion of any blood products. This improper platelet transfusion depletes platelet reserves, thereby impacting patients with a true need for transfusion support. This will require more replacement blood donations than regular non-replacement voluntary donors to maintain adequate platelet stock in the blood center. Random donor platelets are prepared for whole blood donations (350 ml or 450 ml), which, when transfused, will result in a rise in platelet counts of up to 5,000 per cumm per unit of RDPs. Hence, the patients will have to be transfused with more than one unit of RDP at a time (usually 4 to 6 units of RDPs for adults).

This results in the patients getting exposed to more than one donor's blood products, which results in higher risks of getting transfusion-transmitted infections (TTIs) and other side effects related to transfusion of blood products (Muralidhar, Poojari, and Bilal 2021). In India, NAT (Nucleic acid testing) is yet to be implemented in all blood centers, mostly due to cost factors. Currently, most blood centers rely on TTI screening tests, where CLIA and rapid tests are being used, which are less sensitive than NAT. This is another reason to avoid unnecessary transfusion of all blood products and to rely more on regular voluntary blood donors rather than replacement blood donors. Besides the TTI-screened infections, other infections can also be transmitted via platelet concentrates, which are otherwise not routinely screened (Etchells et al. 2018).

The transfusion of any blood products may lead to various adverse reactions, including allergic reactions, TRALI, TACO, FNHTR, hemolytic transfusion reactions. (Etchells et al. 2018) and alloimmunization(Isharat et al. 2022). The presence of leukocytes in the platelets will result in an increased risk of viral infections like Cytomegalovirus, Human Herpes virus, Epstein Barr virus, and Human T-lymphotropic virus (HTLV) (Muralidhar, Poojari, and Bilal 2021).

Thus, there has to be optimal usage of all blood products, especially platelets in Dengue patients. This is more important during Dengue epidemics when there are increased demands. There is a need to minimize unnecessary transfusions and to practice judicious use of a scarce resource. This can be achieved by strictly following the transfusion guidelines and proper prospective auditing from the blood center for each transfusion request. For this, the platelet or any blood requests being sent to the blood center should document the proper indications for the requests. Hospital transfusion committee has very important function in ensuring that the transfusion guidelines are followed strictly. Proper and regular educational reviews and clinical evidence-based transfusion practices will reduce the incidence of inappropriate transfusions (Cameron et al., 2007).

Regular auditing of the platelet transfusion practice is required to detect the inappropriate indications. Prospective auditing will be the best method to identify the indications that deviate from the national transfusion guidelines and intervene to prevent the unnecessary transfusion (Estcourt et al. 2017). Proper educational interventions among the clinical specialities will bring about a tremendous improvement in appropriate utilisation of blood products (Cameron et al. 2007).

CONCLUSION

In this study, we found that a large portion (41%) of the platelet transfusions for Dengue cases were inappropriate. In Haemodynamically stable Dengue patients who have no bleeding risk factors, prophylactic platelet transfusion support should be avoided. Irrational transfusion of the platelets will expose the patients to risks of TTIs and other transfusion-associated adverse reactions. This highlights the need for proper auditing and educational intervention among the clinicians. The latest national transfusion guidelines have to be adopted by the hospital transfusion committee and implemented within the hospital to ensure best transfusion practices. Regular auditing will be necessary to maintain the best transfusion practices within the hospital. Proper coordination and communication between the clinicians and transfusion medicine is essential for ensuring rational use of blood products.

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