

# Limited Role of Platelet Transfusion in Dengue Management and the Value of Reticulocyte Production Index as a Measure of Clinical Improvement

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## Abstract

**Introduction:** Dengue hemorrhagic fever is a painful, debilitating mosquito-borne disease caused by one of the four closely related dengue viruses. These viruses are related the viruses that cause West Nile infection and yellow fever. An estimated 390 million infections occur worldwide with about 96 million resulting in illness. Dengue is characterized by fall in platelet count and rise in the hematocrits. This could be due to increase in plasma capillary permeability. If the platelet count falls critically low (<10,000/cumm), the physicians opt to go for fresh platelet transfusion even if it's signs such as subcutaneous petechial hemorrhages are absent. One of the biggest challenges that treating physicians face today in the treatment of dengue fever is, have the ability to tell if the patient's bone marrow is adequately healthy enough to regenerate the depleted blood platelet elements.

**Methods:** This was an open-labeled observational study to show that platelet transfusion has a limited role in determining the clinical outcome in a patient suffering from dengue. This was an open-labeled observational study conducted during the period of April-September 2016 on NS1 antigen-positive patients with high-grade fever (103°-104° F). Comparison was made between the hemoglobin, hematocrits, and platelet counts of patients when they first arrived, and later, comparison was made between the platelet counts and reticulocyte production indices (RPIs) of the patients on 3 consecutive days after the treatment was complete and the patients were afebrile.

**Results:** It was concluded that on day 1 after becoming afebrile, platelet count 35,000-40,000/cu were in 10 patients (9.26%), platelet count 30,000-35,000/cu in 42 patients (38.89%), and platelet count 25,000-30,000/cu in 56 patients (51.85%). On day 2 after becoming afebrile, platelet count 35,000-40,000/cu were in 8 patients (7.41%), platelet count 30,000-35,000/cu in 36 patients (33.33%), and platelet count 25,000-30,000/cu in 64 patients (59.26%). On day 3 after becoming afebrile, platelet count 35,000-40,000/cu were in 56 patients (51.85%), platelet count 30,000-35,000/cu in 42 patients (25.93%), and platelet count 25,000-30,000/cu in 24 patients (22.22%). The RPI of the same patients on same occasion that on the day 1, RPI 2.5-3.5 in 11 patients (10.19%), RPI 3.5-4.5 in 74 patients (68.52%), RPI 4.5-5.5 in 22 patients (20.37%), and RPI >5.5 in 1 patient (0.93%). On the day 2 after being afebrile, RPI 2.5-3.5 in 2 patients (1.85%), RPI 3.5-4.5 in 83 patients (76.85%), RPI 4.5-5.5 in 21 patients (19.44%), and RPI >5.5 in 2 patients (1.85%), and on the day 3, RPI 2.5-3.5 in 0 patient (0.00%), RPI 3.5-4.5 in 92 patients (85.19%), RPI 4.5-5.5 in 14 patients (12.96%), and RPI >5.5 in 2 patients (1.85%).

**Conclusion:** The study showed that there was no significant improvement in the clinical outcome of patients who received platelet transfusion during the course of treatment. The RPIs of the patients became high even before the rise in platelet counts was observed in the recovering afebrile patients. It could be used as an inexpensive surrogate marker for assessing the recovery of the patient after the fever subsides.

**Key words:** Dengue, Platelet transfusion, Reticulocyte production index, Thrombocytopenia

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**Month of Submission :** 01-2017  
**Month of Peer Review :** 02-2017  
**Month of Acceptance :** 02-2017  
**Month of Publishing :** 03-2017

## INTRODUCTION

Dengue hemorrhagic fever is a painful, debilitating mosquito-borne disease caused by one of the four closely related dengue viruses. These viruses are related the viruses that cause West Nile infection and yellow fever. An estimated 390 million infections occur worldwide with

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about 96 million resulting in illness. Most cases occur in tropical areas of the world with the greatest risk occurring in the Indian subcontinent and South East Asia. Dengue fever endemic to the city of Surat in Gujarat.

Dengue is characterized by fall in platelet count (thrombocytopenia), leukopenia, and rise in the hematocrits.<sup>1</sup> This could be due to increase in plasma capillary permeability. If the platelet count falls critically low (<10,000/cumm), the physicians opt to go for fresh platelet transfusion even if it's signs such as subcutaneous petechial hemorrhages are absent.

One of the biggest challenges that treating physicians face today in the treatment of dengue fever is, have the ability to tell if the patient's bone marrow is adequately healthy enough to regenerate the depleted blood platelet elements. On discharge, the study of reticulocyte production index (RPI) could be used as a potential surrogate marker to indicate sufficient bone marrow regenerative capacity. This would then reassure the treating physician that the platelet count would come back to normal, post-discharge. This would also ensure that the patient would not go into complete bone marrow failure.

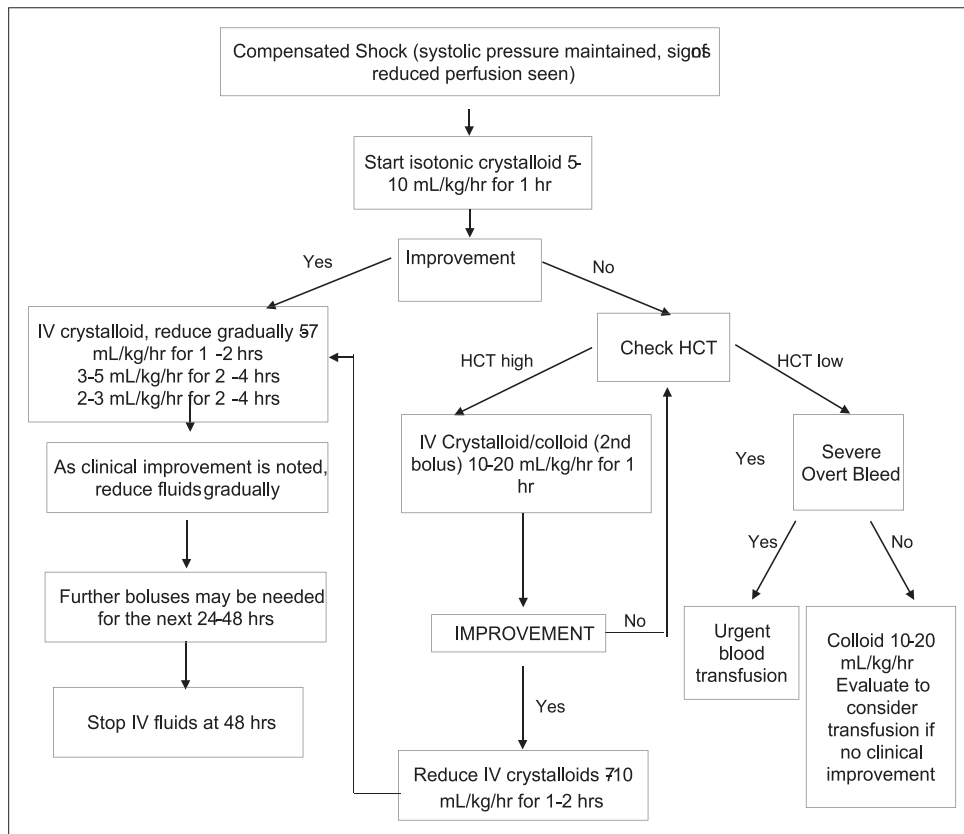
In this study, we investigate the effect of platelet transfusion on the clinical outcome of the patients.

We also assess the utility of RPI for assessing the improvement of patients who are recovering from dengue and are afebrile. The study that was conducted also had the scope to decrease the duration of hospitalization and prevent any exposure to unwanted nosocomial infections. In addition, stored or processed blood products are generally far from a high standard and pose a substantial risk of transfusion reactions and transmission of infectious diseases.<sup>2</sup>

## METHODS

This was an open-labeled observational study. Samples were collected from various hospitals and nursing homes in Surat and processed at Tejas Clinical Laboratory, Surat, during the period of April-September 2016 on NS1 antigen-positive patients with high-grade fever (103°-104° F). 3,112 cases of high-grade fever were reported, out of which 108 tested positive for NS1 dengue antigen.

Platelet counts, hematocrits, and hemoglobin were tested for all patients at the time of diagnosis. All patients were managed by the standard fluid management protocol as mentioned in standard textbooks (Flow Charts 1 and 2).



Flow Chart 1: Management of dengue with compensated shock

**Inclusion Criteria**

1. Clinical diagnosis of dengue (provisional diagnosis).
2. High-grade fever.
3. NS1 positivity was the inclusion criteria for the study.

**Exclusion Criteria**

1. Comatose patients.
2. Patients with comorbidities.

The INTERCEPT blood system was deployed rapidly. This demonstrates the utility of the INTERCEPT blood system to facilitate the availability of apheresis-derived pathogen and leukocyte inactivated platelet concentrates while reducing the risks of transfusion-transmitted infections.<sup>3</sup> Hence, their platelet counts and RPI were done on 3 consecutive days after the patients became afebrile and were showing clinical improvement. Most patients became afebrile within 7-10 days. The final readings were taken as the end point for the study.

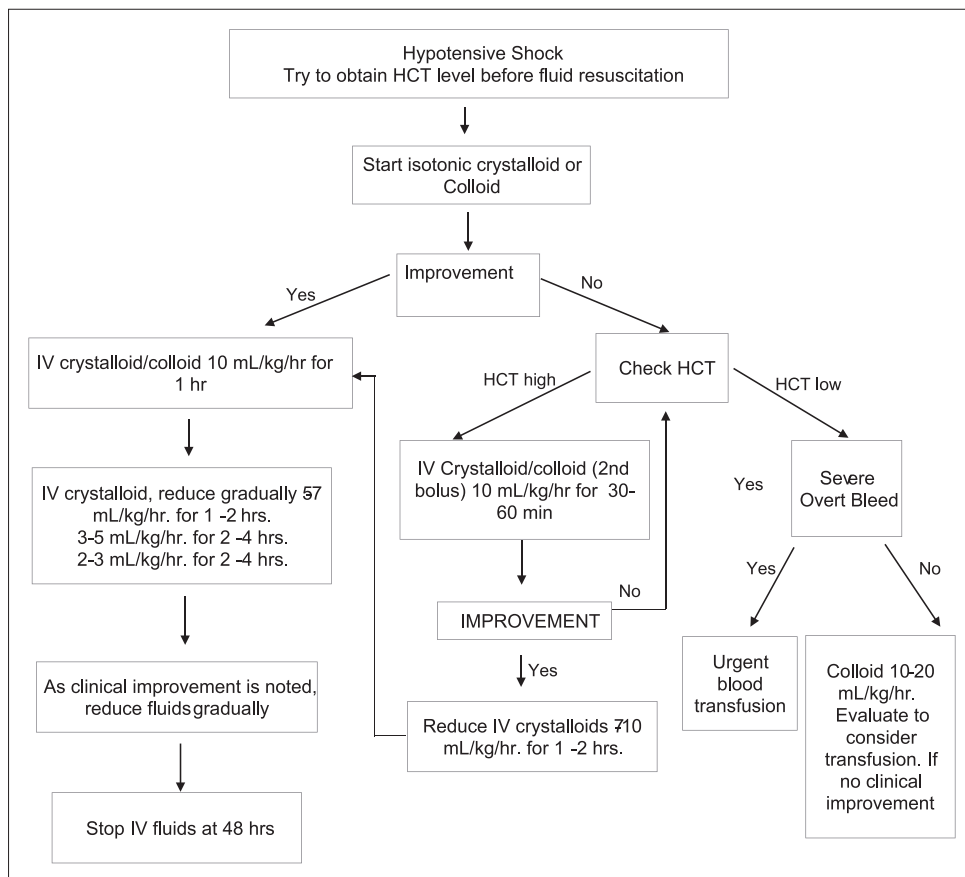
**RESULTS**

From the Tables 1 and 2, author found that 3112 patients admitted with the history of fever in only 108 patients were NS1 positive, i.e., was 3.47%. Moreover, the patients

whose platelets counts were more than 10,000/cu were 103 which was 95.37% while those having platelets more than 10,000/cu were only 5 patients (4.63%).

From Table 3, it was concluded that on day 1 after becoming afebrile, platelet count 35,000-40,000/cu were in 10 patients (9.26%), platelet count 30,000-35,000/cu in 42 patients (38.89%), and platelet count 25,000-30,000/cu in 56 patients (51.85%). On day 2 after becoming afebrile, platelet count 35,000-40,000/cu were in 8 patients (7.41%), platelet count 30,000-35,000/cu in 36 patients (33.33%), and platelet count 25,000-30,000/cu in 64 patients (59.26%). On day 3 after becoming afebrile, platelet count 35,000-40,000/cu were in 56 patients (51.85%), platelet count 30,000-35,000/cu in 42 patients (25.93%), and platelet count 25,000-30,000/cu in 24 patients (22.22%).

Author found the RPI of the same patients on same occasion and draw Table 4 and concluded that on the day 1, RPI 2.5-3.5 in 11 patients (10.19%), RPI 3.5-4.5 in 74 patients (68.52%), RPI 4.5-5.5 in 22 patients (20.37%), and RPI >5.5 in 1 patient (0.93%). On the day 2 after being afebrile, RPI 2.5-3.5 in 2 patients (1.85%), RPI 3.5-4.5 in 83 patients (76.85%), RPI 4.5-5.5 in 21 patients (19.44%), and RPI >5.5 in 2 patients



**Flow Chart 2: Management of severe dengue with shock**

**Table 1: At the time of diagnosis**

Parameters	Number of patients (%)
Patients in which fever present	3112 (100.00)
NS1 positive patients	108 (3.47)

**Table 2: Treatment, the patients, received**

Parameters	Number of patients (%)
NS1 positive patients	108 (100.00)
Patients whose platelet counts were more than 10,000/cumm	103 (95.37)
Patients whose platelet counts were less than 10,000/cumm	5 (4.63)

**Table 3: Platelet count of patients on 3 consecutive days after they became afebrile**

Platelet count	Number of patients (%)		
	Day 1	Day 2	Day 3
35,000-40,000/cu	10 (9.26)	8 (7.41)	56 (51.85)
30,000-35,000/cu	42 (38.89)	36 (33.33)	28 (25.93)
25,000-30,000/cu	56 (51.85)	64 (59.26)	24 (22.22)
	108 (100.00)	108 (100.00)	108 (100.00)

**Table 4: RPI values of the patients during the 3 days mentioned in Table 3**

RPI	Number of patients (%)		
	Day 1	Day 2	Day 3
2.5-3.5	11 (10.19)	2 (1.85)	0 (0.00)
3.5-4.5	74 (68.52)	83 (76.85)	92 (85.19)
4.5-5.5	22 (20.37)	21 (19.44)	14 (12.96)
>5.5	1 (0.93)	2 (1.85)	2 (1.85)
	108 (100.00)	108 (100.00)	108 (100.00)

RPI: Reticulocyte production index

(1.85%), and on the day 3, RPI 2.5-3.5 in 0 patient (0.00%), RPI 3.5-4.5 in 92 patients (85.19%), RPI 4.5-5.5 in 14 patients (12.96%), and RPI >5.5 in 2 patients (1.85%).

## DISCUSSION

The study showed that 3112 patients had fever, but when N1 test was done, only 108 patients were found positive for NS1; it was 3.47% of total cases of fever studied. The study showed that 103 patients recovered from just standard fluid management protocol. Out of these patients, five patients had critically low platelet counts (<10,000/cumm). They still did not have much cutaneous bleeding. These patients received platelet transfusion. Platelet transfusion for the most part is unnecessary for clinical management of a diagnosis of dengue because they may lead to unwanted transfusion-transmitted infection. On the other hand, a fluid and electrolyte management protocol prescribed by

the WHO, and standard textbooks are adequate as therapy in these patients.

Despite the falling platelet count in all patients of dengue, we observed that the clinical features of lack of mucocutaneous bleeding served as our biggest clue for not transfusing patients with platelets.

Therefore:

1. Platelets were given only when we saw evidence of clinical bleeding.
2. During the recovery phase, we used RPI as the surrogate marker for improvement in bone marrow function. The results showed that there was a good correlation between the increase in RPI and increase in post-dengue platelet count.

During the recovery phase of dengue, there is often a time period, in which the patient becomes afebrile and the platelet counts become normal. Hence, to understand if the bone marrow starts functioning normally, the best option would be to perform a bone marrow biopsy and study megakaryocytes. However, this method is invasive, painful, and expensive, and it causes immunocompromised patients, susceptible to infections. For this reason, we decided to use RPI which is an equally accurate surrogate marker and is minimally invasive. It also gives a proper indication of the functionality of the bone marrow.

During the assessment of the RPI of all 108 patients, we found that the RPI had increased in all the patients during a period of 3 days. We also determined that RPI was a reliable laboratory parameter which appeared even when the platelet counts of the patients had not yet increased to normal values.

RPI was a good surrogate marker to predict that those patients with an RPI greater than the cutoff criteria indicated a good bone marrow regenerative capacity and reassured the physicians that the platelet count would eventually go upon discharge.

- On day 1 after become afebrile, when platelet counts were low, RPI values had returned to normal for most patients.
- On day 2 after become afebrile, when the platelet counts dropped for many patients, the RPI values were still rising.
- On day 3 after become afebrile, the platelet counts showed improvement for all patients while the RPI values remained high.

While Ahmed *et al.* had found platelet increment on the 7<sup>th</sup> day while Francisca *et al.* observed only by 11 days<sup>4,5</sup> of disease. Suman *et al.*<sup>6</sup> had also found that immature platelet fraction is an additional parameter that can be monitored to predict platelet recovery so that prophylactic platelet

transfusion can be deferred and also the hazards associated with it, supporting our study. Prophylactic platelet transfusion in clinically stable dengue fever patients with a platelet counts more than 10,000/cumm is not indicated.<sup>7</sup>

## CONCLUSION

RPI was measured after the treatment to evaluate the prognosis of the patients when they were afebrile, and their other blood parameters were still low. The study showed that there was no significant improvement in the clinical outcome of patients who received platelet transfusion during the course of treatment.

The RPIs of the patients became high even before the rise in platelet counts was observed in the recovering afebrile patients. It could be used as an inexpensive surrogate marker for assessing the recovery of the patient after the fever subsides.

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**How to cite this article:** Managoli N, Garg N, Raheja R, Jacob AJ, Atodaria K, Patel F, Desai I, Kumar L. Limited Role of Platelet Transfusion in Dengue Management and the Value of Reticulocyte Production Index as a Measure of Clinical Improvement. *Int J Sci Stud* 2017;4(12):187-191.

**Source of Support:** Nil, **Conflict of Interest:** None declared.