

CASE REPORT

Use of papaya leaf extract in neonatal thrombocytopenia

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Key Clinical Message

Thrombocytopenia is a common condition in neonates. Neonatal thrombocytopenia can cause serious complications such as intraventricular hemorrhage. Papaya leaf extract may be a safe and effective therapy in persistent refractory neonatal thrombocytopenia. Papaya leaf extract was effective for improving platelet count in our baby with persistent thrombocytopenia. However, with no previous evidence of its use in neonates, its use is still experimental and should only be considered in refractory cases after team meeting and detailed discussion with family.

1 | CASE PRESENTATION

Thrombocytopenia in a neonate is a problem with serious complication like intraventricular hemorrhage, if not detected and treated early. Papaya leave extract is being used in pediatric and adult age group patients for the management of thrombocytopenia. However, its effect has not been studied in newborn. Papaya leave extract can prove to be cheap, effective and safe method for improving platelet count in neonatal thrombocytopenia. We report the use of papaya leave extract in a preterm low birthweight newborn with persistent thrombocytopenia not responding to conventional management. The probable cause of thrombocytopenia was sepsis in our index case. Papaya leave extract was given in a dose of 20 mg/kg/dose three times a day. Time required to achieve normal platelet count was 7 days. No side effects like abdominal distension, rashes, vomiting were observed. The patient is under regular follow-up and at 18 months of age, he is thriving well. To the best of our knowledge, this is the first case report on use of papaya leave extract for thrombocytopenia in a newborn.

A male baby 1.73 kg was born at 30 6/7 weeks of gestation to a 38 years old Rh isoimmunised O negative G5P4A0L2 mother with two live female babies and two intrauterine deaths. Present pregnancy was booked and supervised. Mother received intrauterine blood transfusion for fetal anemia at 24 weeks of gestation. Anti D was administered in present pregnancy and mother received adequate steroid coverage. The baby was delivered by emergency cesarean section in view of fetal distress. He did not cry at birth, had APGAR scores of 3, 6, 9 at 1, 5 and 10 minutes, respectively. The initial steps of resuscitation

were done followed by bag and mask ventilation for 30 seconds resulting in improvement of the heart rate. As the baby had retractions and grunt, he was managed with continuous positive airway pressure (CPAP) and one dose of surfactant. As respiratory distress settled, baby was weaned off from CPAP on day 5 to low flow oxygen. Baby developed thrombocytopenia from day one of life ($35\ 000/\text{mm}^3$) for which multiple platelet transfusions were given. There were petechial spots all over the body (Figure 1). Furthermore baby received phototherapy for 5 days, IVIG (intravenous immunoglobulin) and two exchange transfusions were carried out for hyperbilirubinemia on day 1 and 2 as per unit protocol. He also received 21 days of antibiotics for meningitis and antifungal therapy for 10 days. However, platelet count continued to be low, and therefore, maternal derived platelets were transfused twice, keeping alloimmune thrombocytopenia as a possibility as the maternal platelet count was normal. The workup for alloimmune thrombocytopenia was negative and there was no response to maternal derived platelets. As the other two cell lines, WBC's and PCV were normal, bone marrow aspiration was not done. The probable cause of thrombocytopenia in the index case could be sepsis, bacterial or fungal although both bacterial and fungal cultures were sterile. The ultrasound of abdomen and echocardiography were done to rule out thrombus associated consumptive coagulopathy but both turned out to be normal. (Table 1) Having been in tight corner with failure to treat thrombocytopenia, a departmental board meeting was called to decide upon further therapy and role of papaya leaf extract was discussed. All members agreed upon the therapy with papaya leaf extract and also to stop the therapy

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FIGURE 1 Neonate with petechiae

if any evidence of side effects was noted. An informed parent consent was obtained from the parents. Syrup caripil (papaya leave extract by micro laboratory, a Bengaluru-based pharmaceutical company) was started on day 23 of life with utmost care and vigilant monitoring. The drug was started at 20 mg/kg/dose three times a day as the dose for adults as per manufacturer recommendations is 3300 g/d and assuming average adult weight to be around 60 kg it comes around 50 mg/kg/d. Platelet count was repeated every day after starting the therapy till 7 days and then twice a week. After the start of medication, there was a gradual increase in platelet count (Figure 2). Platelet count on the day of starting of syrup caripil was 45 000 and on day 30 of life, platelet count became normal (1, 50 000/mm³). No adverse effects were noted. Caripil was tapered and stopped on day 41 of life as platelet count was persistently above normal. After stopping the drug platelets did not show significant decrease. Baby was discharged on day 45, with platelet count of 1, 59 000/mm³. Hearing screen and retinopathy of prematurity screen were normal. Neurosonogram and metabolic profile were also normal. The infant is under regular follow-up and is doing well. At 18 months of life, baby is thriving with a platelet count of 3, 80 000/mm³. No adverse effects of the drug were noted during the follow-up period.

2 | INVESTIGATIONS

Table 1.

3 | DISCUSSION

The possible mechanism of action includes, papaya leave extract has membrane stabilizing property and could possibly prevent platelet lysis.¹ It has been found that these extracts increase the ALOX 12 (Arachidonate 12-Lipoxygenase, 12S Type) activity by 15-fold and PTFAR activity (Platelet-Activating Factor Receptor) by 13-fold to 14-fold which consequently increases the platelet production.^{1,2} Furthermore, it has been reported that flavonoids of *Carica papaya* leaf extract can inhibit a protease involved in viral assembly.² The other possible mechanisms reported are that the leaf extract of *C. papaya* has antioxidant and free radical scavenging property which can help in the prevention of hemolysis and bleeding.³ The role of Papaya leaf extract has been widely studied in adult and paediatric age group patients for treatment of thrombocytopenia mainly for dengue.^{2,3} However, there is no study or case report on its efficacy and safety in neonates. In a pilot study conducted in Sri Lanka on 12 patients suspected to have dengue, papaya leaf was found to cause an increase in platelet count and total white blood cell count.⁵ In a case report published in BMJ on use of papaya leave extract in 10-year-old and 14-year-old child with dengue, recovery time to achieve normal platelet count was 12-48 hours.⁶ Duration of treatment was not reported in this case report. Kala et al identified 5 patients with dengue who were given papaya leaf extract. They found an increase in platelet count within 24 hours of treatment.⁷ In our case, dose of drug was decided on the basis of reported literature, manufacturer guidelines and was kept on lower side to avoid any unwanted side effects.^{5,6} A recent metanalysis has also revealed a beneficial response of papaya leaf extract in treatment of thrombocytopenia.² The most probable cause of thrombocytopenia in our case was sepsis. The use of papaya

C reactive protein	6 mg/dL (>1 mg/dL positive)
Total leukocyte count	Before papaya leaf extract 4800/mm ³ and after papaya leaf extract therapy 12 400/mm ³
Packed cell volume	42, was maintained and required no further transfusion after starting the drug
CMV PCR	Negative
Urine routine examination	Normal
Echocardiography	Normal
Neurosonogram	Normal
Blood, urine cultures	Sterile
Ultrasound abdomen	Normal

TABLE 1 Investigations

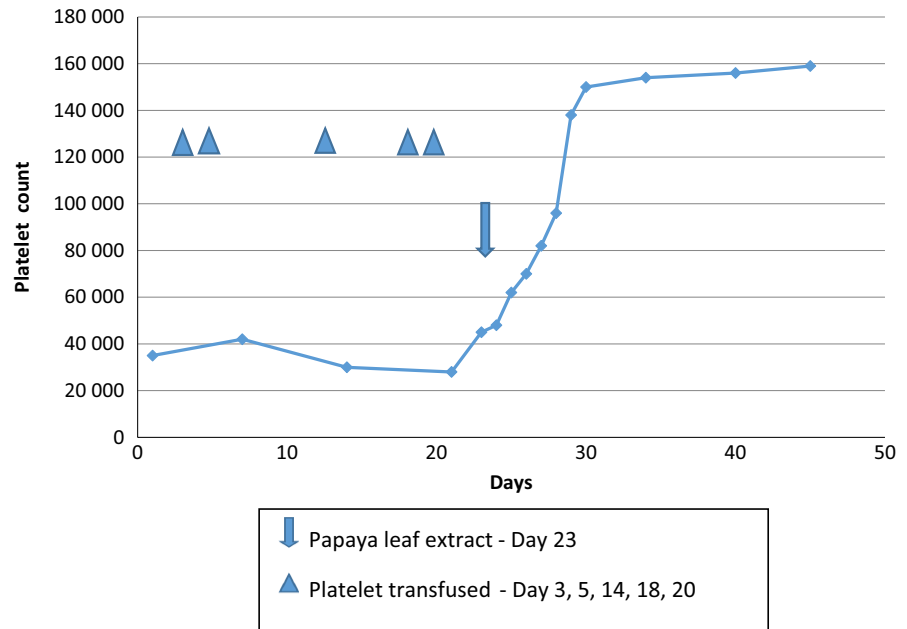


FIGURE 2 Platelet count before and after giving Papaya leaf extract

leaf extract is still experimental till dose, indication and other aspects are well defined. Nonetheless, it can be used as a last resort in refractory cases. It needs to be seen whether the papaya leaf extract is useful for sepsis-associated thrombocytopenia in large multicenter RCT.

4 | CONCLUSION

Thrombocytopenia is a common condition in neonates. Neonatal thrombocytopenia although rare can cause intraventricular hemorrhage. Papaya leaf extract may be a safe and effective therapy in persistent neonatal thrombocytopenia but needs more robust evidence.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

AP, NM wrote the initial manuscript. GG, AP, did the critical appraisal. AP did the final corrections.

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