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Immature Platelet Fraction: A Preliminary Approach to Diagnose the Cause Associated to Neonatal Thrombocytopenia

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Abstract

The immature platelet fraction can be defined as a parameter, which gives a measure of young platelets present in the blood stream. The IPF can be measured by two diagnostic parameters; i.e. the absolute immature platelet count and the fraction of immature platelet count associated to mature platelets. When there is an increased production of platelets by the bone marrow, there is a rise in the level of IPF, therefore, measuring the IPF can estimate the production of platelets in the bone marrow, hence IPF can serve to be of a high clinical utility in the diagnosis of thrombocytopenia. It can serve as a diagnostic tool, for distinguishing the cause of thrombocytopenia between bone marrow failure/suppression or other non-immune causes such as sepsis. It can be a useful tool for understanding the platelet kinetics in patients with thrombocytopenia.

Introduction

Neonatal Thrombocytopenia

In the Neonatal Intensive care unit (NICUs), Thrombocytopenia can be considered to be a frequent observation and also in neonates who are otherwise healthy. Thrombocytopenia in the neonates with Intrauterine growth restriction or mothers with preeclampsia are useallu mild and self-limiting, and is usually because of their response to stress. Thrombocytopenia, can however lead to various hematological and non-hematological disorders, whose diagnosis and management becomes challenging. From rare inherited disorders of platelet production to extremely common acquired causes such as immune mediated thrombocytopenia and sepsis, there is a wide range of etiologies thrombocytopenia [1].

The IPF is a measurement of the youngest platelets in the circulation and, therefore, reflects the thrombopoietic activity. Thus, measuring the IPF might assist clinicians to identify the kinetic mechanism responsible for the thrombocytopenia, as a step toward diagnosing the exact underlying cause. However, to use the IPF in clinical neonatology, rigorously created specific IPF reference intervals are needed. Among thrombocytopenic neonates, we sought to test the utility of using the IPF parameters to categorize thrombocytopenia as the kinetic result of either reduced platelet production (low or normal IPF) or accelerated platelet consumption (high IPF) [2].

What is Immature Platelet Fraction?

The thrombocytes which are newly released from the bone marrow, are the immature platelets also known as the reticulated platelets. These platelets are characterized by their high concentration of RNA cytoplasm and their relatively large size, and it represents the percentage of immature circulating platelets to the total number of platelets. The analytical standardization of IPF by the automated devices has helped in contributing to the use of IPF in the diagnosis of thrombocytopenia [3]. The indicator of IPF is the Mean Platelet Volume, which is similar to the reticulocyte count in the evaluation of anemia. It is the average size of circulating platelets, that can help in ascertaining the the kinetic mechanism of thrombocytopenia in the neonate. The normal range of MPV is (7.5–9.5 fL), when thrombocytopenia is due to reduced production, and is increased (10–12 fL) when caused due to increased destruction. When the bone marrow produces more immature platelets, there is evidence of relatively larger platelets in response to increased utilisation of platelets. However, the gold standard for the diagnosis of thrombocytopenia is Bone marrow biopsy but is difficult and thus postponed till the infant is out of the neonatal period and so, in such situation the MPV is the best non-invasive alternative [4]. The IPF can be a sensitive measure for evaluating thrombopoietic recovery during aplastic chemotherapy and is suggested to be useful for monitoring patients after chemotherapy and haematopoietic stem cell transplantation.

Role of IPF in Thrombocytopenia

When thrombocytopenia is caused by an increased consumption of platelets, IPF can be used as a non-invasive test of thrombopoiesis. A study done by [4], observed IPF to be higher in cases where thrombocytopenia was caused due to either hyperdestruction of platelets or increased consumption of platelets, as compared to the cases where thrombocytopenia was caused by hypodestruction of platelets. This, can be used to ascertain the cause of thrombocytopenia in clinical practice, and can prove to be a tool for differential diagnosis [4].

In a prospective study done by Himani, et al. observed the role of IPF as an initial tool in the diagnostic evaluation of thrombocytopenia. The study divided thrombocytopenic patients in 2 groups; Hyper-destructive and hypo-productive etiology. The IPF % in hypo-productive group was found to be ranging from 0.2-16.9%, while the range in hyper-destructive group was 2.1-37.7%. Thus, IPF can be used as a simple, inexpensive, rapid, and non-invasive automated marker for the etiology of thrombocytopenia. By differentiating between hypo-productive and hyper--destructive causes of thrombocytopenia, it has a definite role in the initial assessment of the etiology of thrombocytopenia and, hence, can be integrated as a standard parameter to evaluate the thrombopoetic state of the bone marrow [5].

The newly produced platelets that were released by the bone marrow megakaryocytes into the circulation is

represented by the IPF. These newly formed platelets are analogs of reticulocytes that are similarily large, containing elevated amount of cytoplasmic RNA. As and when these new platelets age, the amount of cytoplasmic RNA as well as their size decreases. Studies suggests that the proportion of IPF increases or decreases with the rate of platelet production, and hence proves to be valuable marker of thrombopoietic responses, and indirectly provides a measure of bone marrow function [6].

Due to multifactorial etiologies of thrombocytopenia, the underlying causes of thrombocytopenia becomes challenging. The pathogenesis of thrombocytopenia includes either increased consumption or destruction of platelets by the bone marrow, and this should be appropriately managed by the clinicians. A measure of just the platelet count makes it difficult to diagnose the underlying cause of thrombocytopenia, therefore an estimation of platelet production can help to ascertain whether thrombocytopenia is due to bone marrow failure, which is associated to high bleeding risk or because of increased consumption of platelets, where the possibility of bleeding is less likely. The immature platelets are relatively more reactive that the platelets that are mature because of their high granule content and consist of residual RNA derived from megakaryocytes and are also known as reticulated platelets. The meause of IPF can determine the rate of thrombopoiesis, which further helps in differential diagnosis of thrombocytopenia, without doing a bone marrow examination, which is an invasive method [7]. In a study done by Adly, et al. the median IPF was seen to be significantly higher in patients with thrombocytopenia due to increased destruction of peripheral platelets than in patients having thrombocytopenia due to decreased platelet production [4].

Studies suggests that analyzing the compensatory response of the bone marrow to normalize the platelet count , thus obtaining immature platelets as a result of thrombocytopenia caused due to direct or indirect immune response, can be used while diagnosing the patients with low platelet count [9]. Jean and Serramando, et al. suggests IPF to have a discriminatory power to identify the underlying cause of thrombocytopenia and also demonstrated its ability to ascertain the platelet recovery in thrombocytopenic patients.

A model designed by [10], demonstrated that, with the consumption or destruction of platelets in the periphery, the bone marrow increases its output of immature platelets to compensate the loss of platelets. Once, there is improvement in the platelet count as a result of therapy, there is a corresponding decrease in the immature platelet output, as they return to baseline [10].

IPF in Neonatal Thrombocytopenia

When the circulating platelet counts in the neonates is less than 150x103/μL, it is known as Neonatal thrombocytopenia, and it is considered to be a common abnormality in the neonates admitted in the NICU. The diagnosis of neonatal thrombocytopenia is often associated with multiple factors, and therefore differential diagnosis is wide and distinguishing the causes of thrombocytopenia is imperative, as neonatal thrombocytopenia includes life threatening disorders, which can result in life long complications [11].

Thrombocytopenia can be classified into consumptive thrombocytopenia, where there is increased consumption of platelets and hence elevated production of platelets by the bone marrow and second is, thrombocytopenia due to decreased platelet production due to bone marrow suppression/failure.

A study done by Jagtap, et al. stated that the percentage of immature platelets are increased in consumptive thrombocytopenia, which includes; disseminated intravascular coagulation, infection, Necrotizing Enterocolitis, and the percentage of immature platelets decreases where there is decreased production, in cases like IntraUterine Growth Restriction or Birth Asphyxia. This can help the clinicians to ascertain the etiology in managing thrombocytopenia in the neonates [12].

Summary

The youngest platelets that are measurable in the peripheral blood by the hematology analyzers represents the immature platelets. These platelets are larger in size, with higher RNA content and are recently released from the bone marrow.

The compensatory response of the bone marrow

to normalize the platelet count, thus obtaining immature platelets as a result of thrombocytopenia caused due to direct or indirect immune response, can be used while diagnosing the patients with low platelet count.

Studies done by Jean, et al. and Serramando, et al. suggests IPF to have a discriminatory power to identify the underlying cause of thrombocytopenia and also demonstrated its ability to ascertain the platelet recovery in thrombocytopenic patients.

It is suggested that with the consumption or destruction of platelets in the periphery, the bone marrow increases its output of immature platelets to compensate the loss of platelets. Once, there is improvement in the platelet count as a result of therapy, there is a corresponding decrease in the immature platelet output, as they return to baseline [10].

The immature platelet fraction (IPF) is a laboratory quantification of immature platelets in the circulating blood. Thus, the IPF reflects the state of thrombopoiesis in the way a reticulocyte count reflects the state of erythropoiesis. When thrombocytopenia is due to accelerated platelet destruction, the marrow compensates by releasing younger platelets into the blood, which is recognized by an increase in the IPF.

The causes of neonatal thrombocytopenia can be multifactorial, and cannot be obvious always. These causes can be classified on the basis of platelet kinetics; where, either there is a failiure in the platelet production or there is an increased consumption of platelets. The IPF measures the youngest platelets in circulation, reflecting the thrombopoietic activity, that can help the clinicians to identify the platelet kinetics responsible for thrombocytopenia, which can further help to ascertain the underlying cause of thrombocytopenia; however, IPF references should be specifically created in the field of clinical neonatology, so that it is easier to diagnose the etiology of thrombocytopenia which can help the neonatologists to further implement management strategies [1].

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