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A NARRATIVE REVIEW ON NEUTROPAENIA AND PREMATURE INFANTS

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Abstract

In many newborn infants, neutropaenia is a self-resolving condition. Nevertheless, it is thought that in premature infants, neutrophil formation and function are a little different. Since neutrophils play a crucial role in innate immunity, neonatal neutropenia in premature infants needs to be quickly identified and treated according to the risk factors, especially those of clinical infections. Numerous factors, including maternal and prenatal conditions, congenital syndromes, immune-mediated processes, nosocomial infections, and idiopathic conditions, can contribute to neutropenia in premature infants. However, not all premature infant neutropaenia is clinically significant and frequently does not increase the risk of infection. In this review article, we'll talk about the birth of neutrophils, neonatal neutropenia causes, how premature infants and neutropenia are related, and some effective ways to treat the condition.

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Introduction:-

Leukocytes of the type neutrophils make up more than 50% of the total leukocyte count [1]. Ehrlich created a staining method in 1880 that made it easier to recognize developing phagocytes in the bone marrow, blood, and tissues. The possibility of microscopic examinations of blood cells was made possible by the Erhlich's stains, which led to the definitions of the normal counts, leukopenia, leukemia, neutropenia, and agranulocytosis being made very clear [2]. Invading microorganisms like bacteria and fungi are engulfed by circulating neutrophils, which are the primary type of effector cells in the innate immune system [3, 4]. They are produced at a rate of 5 1010–10 1010 cells/day and have a circulating half-life of 6–8 hours [5]. Normal neutrophil counts in premature infants vary by gestational age at birth and birth weight, despite the fact that in pediatric populations, normal ranges primarily depend on age [1]. The neutrophil count in premature and critically ill infants must therefore be carefully assessed. Although neutropenia is typically a benign condition that resolves on its own in the majority of infants, it can persist and cause a critical weakness in the body's ability to fight off infection in some premature infants. Mature neutrophils are produced as a result of an orderly progression of stem cell proliferation, differentiation, and maturation from myeloblast to fully mature segmented cell [6]. Neutrophils go through three stages of development: multiplication, maturation, and functional. The first stage typically lasts 14 days, the mitotic period is 7 and a half days, the second stage is 6 and a half days, and the last stage is 2 and a half days [6]. The myeloblast, which is found in bone marrow, is the first granulocyte-committed progenitor and develops into promyelocyte. Promyelocytes later

develop into myelocytes [7]. These three stages of cell development all allow for cell proliferation. The outcome of the mitotic division is expected to be two symmetrical cells that either proliferate or undergo further maturation [8]. While fully differentiated mature neutrophils make up the post-mitotic pool, which forms the bone marrow reserve and is available for release, the mitotic pool refers to committed granulocytic progenitor cells that are undergoing proliferation and differentiation [5]. When polymorphonuclear cells (PMNs) are in greater demand, the bone marrow's segmented cells are initially stimulated. As a result, the largely dormant population becomes partially active and produces new segmented cells. The polymorphonuclear cells (PMNs) can be continuously produced as a result of this renewal system [8].

Neutropaenia is defined as an absolute neutrophil count (ANC) that is less than two standard deviations below the statistical mean for age [9] or, alternatively, below the 5th percentile for a population with defined ages [3, 10]. Here, the ANC will be calculated as the automated value of white blood cells count (percentsegmented neutrophils+ percentbands)/100 [11]. The initial investigation carried out by Manroe et al. [10] compiled the reference ranges for blood neutrophil concentrations using the cohort of 434 infants (38 point 9 2 point 4 weeks of gestation). The research found that neutrophil counts peaked between 12 and 14 hours after birth, reaching a minimum of 7,800 cells/mm3 and a maximum of 14,500 cells/mm3, before stabilizing at a lower level of 1,750 total neutrophils/mm3 by 72 hours. 5,400 neutrophils/mm3 was the stable maximum value that was attained after 5 days. Since term and late-preterm infants were better served by the reference ranges, Mouzinho et al. Later, another study was conducted by [12]. The study found that the upper limits of blood neutrophil concentrations were nearly identical to those found by Manroe et al. The lower limit, however, displayed more variations. More recently, Schmutz et al. [11] used 30,354 complete blood count records to conduct research on infants born between 23 and 42 weeks of gestation. In his study, the typical range of ANC was between 2700-13,000/L (5th-95th percentile) for infants more than 36 weeks of gestation, between 1000-12,500/L for infants 28–36 weeks of gestation, and between 1300–15,300/L for infants less than 28 weeks of gestation during 72–240 hours after birth. When compared to the ranges that Manroe and Mouzinho both reported, ANC's upper limits were noticeably higher.

Neutropaenia in Premature Infants

Premature birth is defined as birth prior to 37 completed weeks of gestation [13]. Premature births account for 11% of deliveries worldwide [14]. China comes in the second rank after India with 1,172,300 premature infants among the 10 countries having the majority of premature births [15]. Similarly, neutropenia is amongst the most frequently identified abnormalities in neonatal wards and neonatal intensive care units (NICUs). Among the total NICU admissions, approximately 8% of the newborn infants are detected with blood neutrophil counts <1000/μL and 6-58% of premature infants are known to have decreased blood neutrophil counts on at least one occasion [16]. The incidence of neutropenia varies by ethnicity, gestational age, and growth patterns. It is inversely proportional to birth weight and gestational age [17], whereas directly proportional to the grade of hypertension in mothers [12, 18, 19]. Female sex, high-altitude delivery, and mode of delivery of the newborn infants are other associated risk factors [17]. Since the immune systems of premature infants have a relatively smaller pool of neutrophils and monocytes, the potential of these cells to destroy pathogens are impaired and also T-cell activation is limited because of the lower production of cytokines. Consequently, this leads to a decrease in the ability of these cells to combat bacteria and detect viruses in cells compared to mature infants [20-22]. Though a range of common prenatal and postnatal events accompanying premature birth possess an ability to modulate immunity [20], exposure to labor and vaginal delivery have been associated with improved neutrophil function possibly because of immune priming in premature infants [17].

Causes of neonatal neutropaenia

Neutropaenia can be due to varied reasons. The three mechanisms-decrease in the production rate of neutrophils, excessive margination of neutrophils, and increase in destruction rate or combinations of these are considered to be the main reasons [23].

1. Decreased neutrophil production

1. Maternal and pre-natal conditions-maternal hypertension, pre-eclampsia, pregnancy-induced hypertension, intrauterine growth restriction
2. Donors of twin-twin transfusions
3. Infants with Rh hemolytic disease
4. Chronic neutropenia in bone marrow failure syndromes (Kostmann syndrome, Reticular dysgenesis, Cyclic neutropenia, Barth syndrome, Schwachman-Diamond syndrome, Cartilage-hair hypoplasia)

5. Inborn errors of metabolism
6. Glycogen storage disease type 1b, Organic acidemias
7. Viral infections
8. Rubella, Cytomegalovirus (Intrauterine infections)
9. Copper deficiency
10. Alloimmune neutropenia associated with anti-NB1 antibodies**.**

2. Increased neutrophil destruction (utilization)

1. Bacterial or fungal sepsis (including necrotizing enterocolitis)
2. Immune-mediated (alloimmune neutropenia of the newborn, autoimmune neutropenia of infancy, and isoimmune or neonatal autoimmune neutropenia)**.**
3. Excessive neutrophil margination
4. Drug-induced Neutropenia
5. Others
   i
6. Idiopathic Neutropenia of Prematurity**.**

Clinical management of neutropenia in premature infants

Any neutropenia that lasts longer than five days or in particular has an ANC less than 500/L should be thoroughly evaluated [17, 24], as the risk of infection is directly correlated with the duration and severity of neutropenia in premature infants. In the majority of premature infants, neutropenia resolves quickly if the patient survives. As an illustration, the neutropenia that usually accompanies PIH typically goes away in 3 to 5 days. If neutropenia lasts longer than 2 or 3 days in an infant with sepsis, however, a second evaluation should be taken into account. It is still debatable whether or not to administer prophylactic antibiotics to neutropenic infants because doing so could result in fungal sepsis or sepsis caused by bacteria with high resistance [24]. In contrast, sepsis should be taken into account when making a differential diagnosis and an appropriate antibiotic therapy should be started in a critically ill infant while waiting for culture results [25]. Numerous therapeutic approaches have been suggested to boost the premature infants' neutrophil production and functionality. Although some treatment plans have not had a great deal of success in treating premature infants, they are still widely used to treat neutropenia in this population, and some more recent medications are currently undergoing clinical trials.

Intravenous immunoglobulin (IVIG):

Intravenous immunoglobulin (IVIG) is a widely used drug in pediatric practice for immune disorders. Numerous researches have been carried out to see the effectiveness of IVIG in the neutropenic premature infants. A Study conducted by Sandberg et al. [26] shows that there is no role of IVIG as prophylactic immunotherapy to improve the immune competence in premature infants for preventing severe neonatal infections. Similarly, a systemic review carried out by Ohlsson et al. [27] concluded that there is no substantial reduction in the mortality during the hospital stay in infants with suspected or proven infection and the study does not recommend the routine administration of IVIG or IgM-enriched IVIG to prevent mortality in infants with suspected or proven neonatal infection. However, recently Liu et al. [28] stated that premature infants could be benefitted from a high dose IVIG (1-2 g/Kg) by avoiding increased inflammation and restoring the balance in the immune homeostasis.

Corticosteroids:

Corticosteroids have been largely used in the management of immune-mediated neonatal neutropenia [29] but the inconsistent outcome does not reassure the use in neutropenic infants. However, according to the study conducted by Bux et al. [30], the response of corticosteroid therapy was better in primary autoimmune neutropenia (AIN). Dexamethasone administration prior to Cardiopulmonary bypass (CPB) results in the reduction in the inflammatory response but absolute neutrophil counts are not affected [31]. Generally, antenatal corticosteroid is recommended for women who are at risk of a premature delivery before 34 weeks of gestation for the fetal lung maturation [32, 33], but the usage of postnatal steroids in premature infants has been frequently associated with detrimental neurodevelopmental outcomes. Likewise, postnatal growth patterns of prematurely born infants are affected by corticosteroid treatment, more by dexamethasone than by hydrocortisone [34], so postnatal steroids should only be reserved for premature infants who remain ventilator-dependent after the first week of life and the dose and duration of the treatment should be the minimum possible required to achieve extubation [35].

Granulocyte Transfusions:
The granulocyte concentrates transfusion has been proposed in the past for newborn infants with severe neutropenia with severe sepsis resistant to antibiotic treatment. However, at present, there are no defined indications in this concern [36]. Granulocyte transfusions may help in acute situations but the long-term benefit remains unclear [17]. According to the Cochrane database systemic review done in 2011, currently, there is insufficient evidence from randomized controlled trials (RCTs) to validate the routine use of granulocyte transfusions in neutropenic and septic infants, so more researchers are encouraged in multicenter trials [37]. Therefore, in view of the probable adverse effects (transmission of infections), it is more appropriate to use recombinant granulocyte growth factors (recombinant granulocyte colony-stimulating factor, recombinant granulocyte-monocyte colony-stimulating factor) [36].

Recombinant granulocyte colony-stimulating factor (rG-CSF) and recombinant granulocyte macrophage colony-stimulating factor (rGM-CSF):
Granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are cytokines that increase the number of circulating neutrophils by stimulating the bone marrow's neutrophil progenitor cells, boost marrow reserve, and decrease neutrophil apoptosis [38, 39]. The mortality rate in infants with septicemia should decrease theoretically as a result of rG-CSF and rGM-CSF. To test this theory, a meta-analysis involving 5 studies was conducted. The results showed that although there was a slight decrease in the mortality rate in rG-CSF/rGM-CSF recipient infants with presumed septicemia, the effect was more pronounced in the group of infants with neutropenia alone [40]. The administration of rG-CSF in premature infants with a clinical diagnosis of early-onset sepsis was associated with a decreased risk of nosocomial infection over the following three weeks as well as an increase in neutrophil concentration in peripheral blood and bone marrow, according to a similar study [41]. However, there was no difference in the overall mortality rate. Miura et al. conducted yet another study. According to [42], a five-day G-CSF therapy period in neutropenic premature infants with clinical sepsis is safe and also shortens hospital stays, but there is no improvement in the mortality rate. Nearly identical outcomes were seen in studies evaluating G-CSF and GM-CSF as intervention therapy in infants with sepsis, which evaluated the prophylactic use of rG-CSF and rGM-CSF treatment. These studies did not show any evident reduction of infectious complications or an improved overall survival rate. Thus, rG-CSF and rGM-CSF are not advised for routine use in premature as well as term infants based on recent findings [43, 44]. However, rG-CSF is very effective at treating immune-mediated disorders and is also helpful in cases of congenital neutropenia [16]. The preferred course of treatment depends on the duration and severity of the neutropenia in cases of maternal preeclampsia and idiopathic neutropenia of prematurity [16, 43].

Pentoxifylline:
In premature infants, pentoxifylline's immunomodulatory property causes a distinct immunological response that leads to quantitative and qualitative differences in the levels of surface marker and cytokine production [45]. When used as an adjunct therapy to antibiotic regimens, pentoxifylline significantly lowers the immature-to-total neutrophil ratio (I/T) and C-reactive protein (CRP) in a cross-sectional study involving 18 very low birth weight (VLBW) premature infants with nosocomial sepsis [46]. The use of pentoxifylline in addition to antibiotics reduces neonatal sepsis mortality without causing any negative side effects, according to a 2015 Cochrane database analysis. To confirm pentoxifylline's efficacy in lowering mortality and morbidity rates in infants with sepsis, however, well-designed multicentre trials are still essential due to the low-quality evidence from the relatively small studies [47]. Pentoxifylline is compatible with common neonatal medications in the NICU when administered via the same intravenous line, according to a significant retrospective cohort study involving 311 premature infants [48]. The use of pentoxifylline as an adjuvant therapy in numerous medical facilities to treat premature infants with illnesses like nosocomial infections has recently increased, but no significant side effects have been reported. So, while it can be said to be a safe drug, more clinical research is required before it can be recommended for use on a regular basis.

Conclusion:-
The apparent decline in neonatal mortality has been significantly aided by recent developments in neonatal medicine. But because premature infants are surviving longer, there are more premature infants with chronic illnesses and disabilities. There are still few and frequently contentious scientific studies focusing on neutropenia in premature infants and the best treatment options for those premature infants. Therefore, we fervently support additional research in this area that tackles the problems with premature infants.

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