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Evaluation of platelet count and indices in adult patients suffered from sepsis

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Abstract
Hemostasis is a dynamic process in which the platelet and the blood vessels play a key role. Platelets also mediate leukocyte movement from the blood stream through the vessel wall to tissues and are capable of forming reactive oxygen species and the oxidative stress that accompanies inflammation can also activate platelets. Platelets ability to influence other cells indicates that they can also play many principle roles in the pathophysiology of diseases. Platelet indices, are a group of derived platelet parameters, obtained as a part of the automatic complete blood count. Emerging evidence suggests that Platelet indices may have diagnostic and prognostic value in certain diseases. Hence, simultaneous measurement of platelet indices (MPV, PDW, P-LCR) will provide a valid instrument for measuring disease.
The present study was done in Department of General Medicine, Patna Medical College and Hospital from Oct 2016 to Feb 2017. This study was aimed to investigate the relation between sepsis and platelets and its indices (MPV, PDW, P-LCR). Total 50 patients were included, out of that 25 cases of Sepsis were enrolled in study group and 25 cases of the normal patients were enrolled as control cases.
Platelet distribution width is an important index in platelet parameters. It along with other platelet indices can give valuable information regarding the mechanism of platelet destruction. Increased variation in Platelet Distribution Width indicates greater platelet heterogenicity along with destruction and splenic pooling. PDW varies inversely with platelet count.

Keywords: platelet count and indices, adult patients, sepsis, etc

Introduction
Thrombocytopenia is a condition characterized by abnormally low levels of thrombocytes, also known as platelets, in the blood. A normal human platelet count ranges from 150,000 to 450,000 platelets per microliter of blood. These limits are determined by the 2.5th lower and upper percentile, so values outside this range do not necessarily indicate disease. One common definition of thrombocytopenia requiring emergency treatment is a platelet count below 50,000 per microliter [1].
Thrombocytopenia usually has no symptoms and is picked up on a routine full blood count (or complete blood count). Some individuals with thrombocytopenia may experience external bleeding such as nosebleeds, and/or bleeding gums. Some women may have heavier or longer periods or breakthrough bleeding. Bruising, particularly purpura in the forearms and petechiae in the feet, legs, and mucous membranes, may be caused by spontaneous bleeding under the skin.
Eliciting a full medical history is vital to ensure the low platelet count is not secondary to another disorder. It is also important to ensure that the other blood cell types, such as red blood cells and white blood cells, are not also suppressed. Painless, round and pinpoint (1 to 3 mm in diameter) petechiae usually appear and fade, and sometimes group to form ecchymoses. Larger than petechiae, ecchymoses are purple, blue or yellow-green areas of skin that vary in size and shape. They can occur anywhere on the body [2].
A person with this disease may also complain of malaise, fatigue and general weakness (with or without accompanying blood loss). Acquired thrombocytopenia may be associated with the use of certain drugs. Inspection typically reveals evidence of bleeding (petechiae or ecchymoses), along with slow, continuous bleeding from any injuries or wounds. Adults may have large, blood-filled bullae in the mouth. If the person's platelet count is between 30,000 and 50,000/mm3, bruising with minor trauma may be expected; if it is between 15,000 and 30,000/mm3, spontaneous bruising will be seen (mostly on the arms and legs) [3].
Thrombocytopenia affects a few percent of newborns, and its prevalence in neonatal intensive care units (NICU) is high. Normally, it is mild and resolves without consequences. Most cases affect preterm birth infants and result from placental insufficiency and/or fetal hypoxia. Other causes, such as alloimmunity, genetics, autoimmunity, and infection, are less frequent [4].
In the case of infection, PCR tests may be useful for rapid pathogen identification and detection of antibiotic resistance genes. Possible pathogens include viruses (e.g. Cytomegalovirus (CMV), rubella virus, HIV), bacteria (e.g. Staphylococcus sp., Enterococcus sp., Streptococcus agalactiae, Listeria monocytogenes, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae,

Pseudomonas aeruginosa, Yersinia enterocolitica), fungi (e.g. Candida sp.), and Toxoplasma gondii. The severity of thrombocytopenia may be correlated with pathogen type; some research indicates that the most severe cases are related to fungal or gram-negative bacterial infection. The pathogen may be transmitted during or before birth, by breast feeding, or during transfusion. Interleukin-11 is being investigated as a drug for managing thrombocytopenia, especially in cases of sepsis or necrotizing enterocolitis (NEC) [5].

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. Common signs and symptoms include fever, increased heart rate, increased breathing rate, and confusion. There may also be symptoms related to a specific infection, such as a cough with pneumonia, or painful urination with a kidney infection. In the very young, old, and people with a weakened immune system, there may be no symptoms of a specific infection and the body temperature may be low or normal, rather than high. Severe sepsis is sepsis causing poor organ function or insufficient blood flow. Insufficient blood flow may be evident by low blood pressure, high blood lactate, or low urine output. Septic shock is low blood pressure due to sepsis that does not improve after fluid replacement [6].

Sepsis is usually treated with intravenous fluids and antibiotics. Typically, antibiotics are given as soon as possible. Often, ongoing care is performed in an intensive care unit. If fluid replacement is not enough to maintain blood pressure, medications that raise blood pressure may be used. Mechanical ventilation and dialysis may be needed to support the function of the lungs and kidneys, respectively. To guide treatment, a central venous catheter and an arterial catheter may be placed for access to the bloodstream. Other measurements such as cardiac output and superior vena cava oxygen saturation may be used. People with sepsis need preventive measures for deep vein thrombosis, stress ulcers and pressure ulcers, unless other conditions prevent such interventions. Some might benefit from tight control of blood sugar levels with insulin. The use of corticosteroids is controversial, with some reviews finding benefit, and others not [8].

Disease severity partly determines the outcome. The risk of death from sepsis is as high as 30%, from severe sepsis as high as 50%, and from septic shock as high as 80%. The number of cases worldwide is unknown as there is little data from the developing world. Estimates suggest sepsis affects millions of people a year. In the developed world approximately 0.2 to 3 people per 1000 are affected by sepsis yearly, resulting in about a million cases per year in the United States. Rates of disease have been increasing. Sepsis is more common among males than females. The medical condition has been described since the time of Hippocrates. The terms "septicemia" and "blood poisoning" have been used in various ways and are no longer recommended [9].

Bacterial virulence factors, such as glycocalyx and various adhesins, allow colonization, immune evasion, and establishment of disease in the host. Sepsis caused by gram-negative bacteria is thought to be largely due to a response by the host to the lipid A component of lipopolysaccharide, also called endotoxin. Sepsis caused by gram-positive bacteria may result from an immunological response to cell wall lipoteichoic acid. Bacterial exotoxins that act as superantigens also may cause sepsis [36]. Superantigens simultaneously bind major histocompatibility complex and T-cell receptors in the absence of antigen presentation. This forced receptor interaction induces the production of pro-inflammatory chemical signals (cytokines) by T-cells [10].

There are a number of microbial factors that may cause the typical septic inflammatory cascade. An invading pathogen is recognized by its pathogen-associated molecular patterns (PAMPs). Examples of PAMPs include lipopolysaccharides and flagellin in gram-negative bacteria, muramyl dipeptide in the peptidoglycan of the gram-positive bacterial cell wall, and CpG bacterial DNA. These PAMPs are recognized by the pattern recognition receptors (PRRs) of the innate immune system, which may be membrane-bound or cytosolic. There are four families of PRRs: the toll-like receptors, the C-type lectin receptors, the NOD-like receptors, and the RIG-I-like receptors. Invariably, the association of a PAMP and a PRR will cause a series of intracellular signalling cascades. Consequentially, transcription factors such as nuclear factor-kappa B and activator protein-1, will up-regulate the expression of pro-inflammatory and anti-inflammatory cytokines [11].

Two sets of blood cultures (aerobic and anaerobic) should be taken without delaying the initiation of antibiotics. Cultures from other sites such as respiratory secretions, urine, wounds, cerebrospinal fluid, and catheter insertion sites (in-situ more than 48 hours) can be taken if infections from these sites are suspected. In severe sepsis and septic shock, broad-spectrum antibiotics (usually two, a β-lactam antibiotic with broad coverage, or broad-spectrum carbapenem combined with fluoroquinolones, macrolides, or aminoglycosides) are recommended. The choice of antibiotics is important in determining the survival of the person. Some recommend they be given within one hour of making the diagnosis, stating that for every hour of delay in the administration of antibiotics, there is an associated 6% rise in mortality. Others did not find a benefit with early administration [12].

Several factors determine the most appropriate choice for the initial antibiotic regimen. These factors include local patterns of bacterial sensitivity to antibiotics, whether the infection is thought to be a hospital or community-acquired infection, and which organ systems are thought to be infected. Antibiotic regimens should be reassessed daily and narrowed if appropriate. Treatment duration is typically 7–10 days with the type of antibiotic used directed by the results of cultures. If the culture result is negative, antibiotics should be de-escalated according to person's

clinical response or stopped altogether if infection is not present to decrease the chances that the person is infected with multiple drug resistance organisms. In case of people having high risk of being infected with multiple drug resistance organisms such as Pseudomonas aeruginosa, Acinetobacter baumannii, addition of antibiotic specific to gram-negative organism is recommended. For Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin or teicoplanin is recommended. For Legionella infection, addition of macrolide or fluoroquinolone is chosen. If fungal infection is suspected, an echinocandin, such as caspofungin or micafungin, is chosen for people with severe sepsis, followed by triazole (fluconazole and itraconazole) for less ill people. Prolonged antibiotic prophylaxis is not recommended in people who has SIRS without any infectious origin such as acute pancreatitis and burns unless sepsis is suspected [13].

Once daily dosing of aminoglycoside is sufficient to achieve peak plasma concentration for clinical response without kidney toxicity. Meanwhile, for antibiotics with low volume distribution (vancomycin, teicoplanin, colistin), loading dose is required to achieve adequate therapeutic level to fight infections. Frequent infusions of beta-lactam antibiotics without exceeding total daily dose would help to keep the antibiotics level above minimum inhibitory concentration (MIC), thus providing better clinical response. Giving beta-lactam antibiotics continuously may be better than giving them intermittently [14]. Access to therapeutic drug monitoring is important to ensure adequate drug therapeutic level while at the same time preventing the drug from reaching toxic level.

Methodology

The present study was done in Department of General Medicine, Patna Medical College and Hospital, from Oct 2016 to Feb 2017. This study was aimed to investigate the relation between sepsis and platelets and its indices (MP, PDW, P-LCR). Total 50 patients were included, out of that 25 cases of Sepsis were enrolled in study group and 25 cases of the normal patients were enrolled as control cases.

Venous blood samples were drawn at the time of admission before initiation of treatment. Estimation of MPV, PDW and P-LCR, were performed in all patients(by Hemogram).All blood samples were processed within 30 minutes of blood collection using an autoanalyser. Clinical history include age, sex, history of precipitating factors (vigorous physical exercise, emotional stress or medical or surgical illness), past history of diabetes, hypertension, smoking, previous episodes of chest pain.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Results & Discussion

Sepsis and septic shock are one of the leading causes of death worldwide. Even though there are several biomarkers available to assessing the prognosis of sepsis, it remains still difficult. The decrease in platelets (thrombocytopenia) is common in severely ill patients, and several studies have reported its association with poor prognosis. Considering the fundamental role of platelets in haemostasis and as markers of disseminated intravascular coagulation, a significant drop in platelet count is alarming in the setting of septic patients, as it is an independent factor predicting death. Hence, we have conducted this study to determine thrombocytopenia and its progression in predicting of prognosis in sepsis.

Thrombocytopenia (TCP) can be due to increased peripheral destruction, inadequate production or abnormal pooling. Clinical methods alone do not always permit a confident assessment of mechanism in individual cases. Platelet volume parameters are the measurements made on peripheral blood platelets and include MPV, PDW and PLCR.

Platelets are small discoid cellular elements which are heterogeneous with respect to size,density,age and metabolic function. The usual adult human has a platelet count between 1.5 - 4.5 lakhs/mm3. Platelet indices or platelet volume parameters mainly include mean platelet volume(MPV),platelet distribution width(PDW) and platelet large cell ratio(PLCR).Automated cell counters have made the platelet count and platelet volume indices - MPV,PDW and PLCR routinely available in most clinical laboratories since the early 1980's. The MPV indicates average size of the platelets and its normal volume is 7.4 -10.4fl. According to recent studies, larger platelets are enzymatically and metabolically more active and have higher thrombotic potential as compared with smaller ones. Hence persons with high MPV are said to be at risk for thrombotic events.

Table 1: Basic Details of Groups

Group	Cases of Sepsis	Control Cases
Age	38- 69	35 – 71
Heart rate	105 ± 22	110 ± 31
Microbiology	25	
Gram negative rods	18	14
Gram positive cocci	5	8
Fungi	2	3
Total	25	25
Infection acquired		
Community	15	19
Hospital	10	6
Total	25	25
Infectious focus		
Pulmonary	11	15
Intra-abdominal	7	3
Urologic	4	3
CNS	2	2
others	1	2
Total	25	25

Table 2

Parameters	Cases of Sepsis	Control Cases
PDW: Platelet Distribution Width	11.62 ± 1.86	12.64 ± 2.93
MPV: Mean Platelet Volume	10.31 ± 0.84	10.67 ± 1.12
PLCR: Platelet larger cell ratio	28.14 ± 6.82	26.39 ± 7.89

Vanderlelie *et al.* 1983 [15] showed that MPV was elevated in 13 of the 25 septicemia patients and returned to normal values as soon as the disease was under control. In 2 different new born cohorts with sepsis by Guida eat al 2003 [16], thrombocytopenia and high MPV appeared to be prominent. MPV was not increased in local infection or sepsis with negative blood culture. They suggested, an elevated MPV indicates that the infection is invasive, systemic and uncontrolled and is related to the severity of the disease and therefore MPV may be a useful assessment tool for prognostic features of septic shock. Chen Hokim *et al.* 2015 [17] revealed a greater increase of MPV in non-survivors of severe sepsis and or septic shock compared with survivors during the first 72hrs after hospitalization and found that an increase in MPV from baseline is an independent risk factor of mortality

Yanxia Gao *et al.* 2014 [18] observed that MPV,P-LCR and PDW were increasing. In an another study Pattrapom T *et al.* 2016 [19], a retrospective study, the rise in MPV and to a lesser extent an increase in P-LCR and PDW, was indicative of a worse prognosis in patients with septic shock. A statistical difference in MPV was seen between the non survivors and the survivors of the septic shock.

The MPV is an average size of platelets. Elevated MPV may indicate endothelial damages as well as platelet activation and is an easily accessible haematological parameter [6] In the clinical study of Nelson and Kehl, it was uncovered that the thrombocyte consumption and MPV values escalated in acute infections [20]. Becchi *et al.* showed in their study that the MPV could be used as an indicator of platelet behavior and malfunction in indirect platelet production and activation during sepsis response. The MPV escalation was found crucial for predicting prognosis in early stage sepsis. Moreover, the MPV values at the moment of application were higher in the deceased patients in comparison to the survivors [21]. In the study of Daniel conducted on 191 patients with sepsis, the increase in the MPV values was found significant in terms of prognosis and mortality [22].

The PDW is a marker indicating the changes indirectly measurable platelet size and the platelet activation [23]. Zhang *et al.* have reported that the MPV and PDW values were valuable for predicting mortality in patients hospitalized in intensive care units [24]. Gao *et al.* have reported that the platelet count decreased and the PDW amounts increased in patients with sepsis, due to this lead to increased mortality rate [25]. In the study of Njoroge *et al.* conducted on 125 cases for the use of haematological parameters for sepsis follow-ups and uncovered that the MPV and PDW escalation was a messenger for mortality [26].

The P-LCR is designated by proportioning the platelet number and larger cell (lymphocyte) number. An escalated platelet number indicates excessive platelet activity caused by destructive pro-inflammatory and pro-thrombotic responses. On the contrary, lymphocytes contribute less for repressing this aggravated inflammatory process and controlling this process [27]. Therefore, for inflammatory and pro-thrombotic cases, the P-LCR is found high as a ratio of these two haematological indices, and it is more simple, convenient and superior in comparison to the thrombocyte or lymphocyte numbers that are used alone [28]. The P-LCR integrates the platelet and haematological indices as a novel indicator of inflammation in various pathological conditions and emerges as a simple and applicable prognosis marker [27-28]. Recent studies reported that the P-LCR was a better indicator for inflammation in comparison to the WBC number [29-30]. Balta and Ozturk have reported that the P-LCR could be used in cardiovascular cases as an inflammatory marker in the clinic [31].

Conclusion

Platelet distribution width is an important index in platelet parameters. It along with other platelet indices can give valuable information regarding the mechanism of platelet destruction. Increased variation in Platelet Distribution Width indicates greater platelet heterogenicity along with destruction and splenic pooling PDW varies inversely with platelet count.

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