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MINI REVIEW

Haematological Changes in Alcohol and Substance Use Disorders- An Overview

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Abstract

Alcohol and Substance use remains a worldwide social problem. There is an increasing awareness that alcoholics and substance abusers do show some haematological abnormalities (e.g., hemoglobin, white blood cells count, mean corpuscular volume, mean corpuscular haemoglobin concentration, red blood cells count, hematocrit). Consequences of these haematological abnormalities can result in serious medical complications. The aim of this paper is to present an overview of haematological changes in alcohol and substance use disorders. This may be beneficial for defining the homeostasis condition of the body, which leads to indications for treatment approaches.

Keywords

Alcohol, Substance use, Hematological changes

Introduction

Substance use disorders cause tremendous burden to health care systems and society world-wide. As per the World Drug Report (2019) [1], about 35 million people worldwide suffer from drug use disorders. Disorders due to illicit drug use accounted for 10.9% of the DALYs caused by mental and substance use disorders and alcohol use disorders accounted for 9.6% [2]. These drugs can be consumed either by inhalation, injection, or by ingestion. Alcohol and Substance use changes the body functions by influencing endogenous constituents of the bodies [3]. These substances, when cross the blood-brain barrier on ingestion, may affect the brain function either depress or stimulate its activity and temporarily alter the chemical milieu of the brain. Long-term use of these addictive substances leads to serious damage to the nervous system and internal organs. Moreover, illicit drug uses are commonly linked with aplastic anaemia, bone marrow repression and variety of systemic disorders [3]. Hence, early diagnosis of these disorders and identification of the complications they result in is important. Haematology is the branch of medicine that deals with blood, blood-forming organs and blood disorders. This article summarizes current information on the haematological changes that are observed in different substance use disorders and the utility of these changes in clinical assessment.

Overview of Substances

Alcohol

Alcohol is the most commonly used worldwide. Alcohol consumption is one of the leading causes of death. Chronic alcohol intake can interfere with various physiological, biochemical and metabolic processes of the blood cells and affect multiple organ systems. Alcohol use, especially in heavy drinkers, can cause different metabolic derangements. Haematological adverse effects of acute and chronic alcohol use result from both direct and indirect effects [4,5]. The direct consequences include toxicity to the blood-forming organs (viz. bone marrow); the blood cell precursors; and the mature Red Blood Cells (RBC's), White Blood Cells (WBC's), and platelets, resulting in fewer than-normal or non-functional mature blood cells.

Alcohol's indirect effects include metabolic or physiological alterations resulting in liver disease and nutritional deficiencies such as folate deficiencies that

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impair the production and function of various blood cells [4-6]. Folate deficiency also has an important role in the pathogenesis and progression of alcohol-related liver disease [7]. Moreover, Liver damage secondary to alcohol abuse also impacts red blood cells and the hemostatic mechanisms. These direct and indirect effects of alcohol can result in serious medical complications among alcohol abusers. For instance, anaemia resulting from diminished RBC production and impaired RBC metabolism and function causes fatigue, shortness of breath, light headedness, and even reduced mental capacity and abnormal heartbeats in alcoholics. It has been found that alcohol interferes with the production and function of white blood cells. The number of WBC's decreases (especially neutrophils) which increases the risk of serious infection. Also, the platelet (PLT) production gets impaired resulting in interference with blood clotting. This may lead to symptoms ranging from nose bleeding to bleeding in the brain (i.e., hemorrhagic stroke). Finally, alcohol-induced abnormalities in the plasma proteins, required for blood clotting can lead to the formation of blood clots (i.e., thrombosis) [4]. Evidence is there to suggest that alcohol abuse can cause bone marrow suppression, or ethanol has cytotoxic effects. These includes myelosuppression that is accompanying with slight reduction in all blood cells, blood loss from gastrointestinal tract, malnutrition etc [8]. Among the mechanisms explored for the effect of alcohol is the formation of adducts by acetaldehyde with cellular proteins [9]. These altered proteins have been postulated to evoke an immune reaction as evidenced by the presence of IgM and IgG antibodies against them. Studies suggest that consumption of alcohol causes changes of Complete Blood Counts (CBC). A study from India shows significant reductions of haemoglobin, RBC, WBC, haematocrit and significant elevations in MCV and MCH among alcoholics [10]. Another study from, India, compared the changes in the complete blood count in 30 young male subjects between 20-40 years of age group who consumed two to three units of alcohol on a daily basis with abstainers of the same age group [11]. The findings suggest that drinking of alcohol even for a short or moderate duration can affect various haematological parameters like platelet count and Mean Corpuscular Volume (MCV). Furthermore, another study from North India examined the haematological profile of alcohol dependent subjects [12]. The results showed an increase in erythrocyte Mean Cell Volume (MCV), Mean Corpuscular Haemoglobin (MCH), and a decreased mean value of RBC, total leucocyte and platelet counts, particularly among those with higher amount of alcohol consumption. In another study from South India the haematological parameters were examined in male alcoholics. The results were in line with the earlier report which suggested that the MCV was increased in the patients with alcohol dependence either co-morbid with tobacco dependence or without, compared to normal subjects [13]. Recently, a cross-sectional study has been published in which comparison of haematological parameters between alcoholics and non-alcoholics were done. The findings indicated that mean RBC count, mean MCH, MCHC were normal among the non-alcoholic group and decreased among moderate alcoholics and more so with severe alcoholics and a similar type of result was also seen with total count and platelet count [14]. A study from Japan attempted to characterise the change in the white blood cell counts with varying alcohol consumption levels as it has been seen that lower number of white blood cells has been associated with a decreased risk for chronic heart disease [15]. The common abnormalities that are associated with alcohol abuse with respect to duration of alcohol abuse and the quantity of alcohol consumed are anemia, leukopenia and thrombocytopenia [8]. Several studies have tried to explain the mechanism through which alcohol causes these changes in blood parameters. Anemia may be caused by a patient's poor nutritional status coupled with poorer access to health care. This resulted in chronic infections causing anemia of chronic disease, through blood loss from gastrointestinal bleeds, through splenic sequestration and destruction of cells in hyper-splenic from portal hypertension [16,17]. The findings suggest that the development of megaloblastic haematopoiesis in alcoholics is due to the induction of folate deficiency. Besides folate depletion, direct toxic effect of alcohol on erythroid precursors is reflected by the presence of normal plasma and erythrocyte folate levels in several patients with megaloblastic change. Another important effect of alcohol is in haematopoiesis in the marrow. Ringed side oblasts are seen in the marrow and the marrow might be hypoplastic or even aplastic [18]. A finding that precedes anemia is macrocytosis, the mechanism of which is not known [19]. This result in cell sizes ranging from 100-110 falls this finding has to be differentiated from megaloblastic anemia in which cell sizes generally exceed that seen in alcohol use. The poor immunity to infections in alcohol dependent subjects may be the result of both the decrease in neutrophil number as well as faulty functioning [20]. The decreased counts may be caused due to marrow hypoplasia or hypersplenism. The effects on the blood platelets are similar with effect on both thrombocyte formation as well as functioning. The platelet count rarely falls below 10,000/$mm^{3.}$ Abstaining from alcohol results in a rebound thrombocytosis in the first two weeks, counts may reach up to 600,000/mm^3 [21]. Alcohol use has also been clearly observed with increased iron stores specially in the liver resulting in an iron overload state [22]. This adds to the oxidative stress that plays a part in the development of hepatic cirrhosis.

Tobacco

Tobacco use remains a global public health problem. Each year, tobacco use is responsible for approximately

8 million deaths worldwide (WHO, 2019) [1]. Tobacco use is known to have effects on haematological parameters such as haemoglobin level and coagulability. It has been found that smokers have a significantly higher level of haemoglobin, haematocrit, MCHC and total and differential leucocyte counts [23,24]. It has also been shown that the increase in haemoglobin level is correlated positively with the duration of smoking. This can be explained by smoking resulting in increased carboxyhaemoglobins levels that causes hypoxemia and as the CO binds with Hb, functional anaemia is produced. The increase in the WBC counts could indicate the effect of release of catecholamines on WBCSs or the inflammation caused by smoking in the respiratory tract. The cessation of smoking for periods longer than one year has shown reversal of increased WBC counts [25]. Although several studies have observed a positive association between smoking and total white blood cell counts, there have been some conflicting results for the subpopulations [23,25,26]. Also, conflicting results have been reported in the association between smoking and thrombocytes and some red blood cell indices too [26-29].

This causes the impaired oxygenation of tissues and change in heamatological parameters Smoking also has significant effects on immunity, some of which are mediated through changes in the functioning of the T lymphocytes. Smokers have decreased number of CD4+ vet cells, while passive smoking increases the number of naïve CD+ vet T cells in peripheral blood [30]. The regulation of immune responses has been studied in smokers with Chronic Obstructive Pulmonary Disease through studying the changes in the sub-populations of helper T cells. It has been found that smokers with COPD have an increased number of Th17 cells, and that smokers with and without COPD had increased number of Th1 and Treg cells [31]. Smoking also adversely effects components of innate immunity. It increases the numbers and alters the distribution of Langerhans cells and dendritic cells in the alveolar parenchyma [32]. The numbers of Natural Killer cells and the cytokines produced by them, such as INF-gamma and TNF alpha are also reduced [33]. It is still uncertain whether tobacco smoking causally influences the hematopoietic system.

Cannabis

There are a number of animal studies that looked into changes in haematological parameters after exposure to cannabis through different routes [34,35]. However, human studies are few and commonly have the limitation of small sample sizes. The effect of cannabis used through the smoking route on haematological parameters has been studied. Oseni, et al. [36] investigated the effect of marijuana smoking on haematological parameters between smokers and non-smokers. The findings suggest that the values observed for total leucocytes, neutrophil, lymphocyte, monocyte and platelet counts, though in normal range, were marginally lower in smokers, whereas values observed for PCV, haemoglobin and eosinophil were marginally higher. A published study from India [37] showed eosinophil counts to be high in 6% of cases, and neutrophil count abnormalities in 7.5% of subjects, which support previous studies on cannabis users [38]. The lymphocyte counts showed a normal level while low mean relative monocyte count was observed [36]. Another study from Pakistan compared Hb concentration, RBC count, WBC count and platelet count between cannabis smokers and healthy controls. They found significant increase in the leucocyte count of cannabis smokers as compared to controls. Also, eosinophils and monocytes values were significantly lower as compared to the control group. The study results showed slightly lower haemoglobin values in cannabis smoker group as compared to control group which could be due to poor nutrition of the smokers [39]. These findings suggest that cannabis usage results in marked differences in some haematological parameters which may lead to inflammation, reduced immunity and ability to fight infections by users. A study from Turkey investigated alterations of the hematologic cells in synthetic cannabinoid users [40]. They found synthetic cannabinoid user group differed significantly from a control group in terms of WBC, DLC, MPV, MCH, MCV and RDW. The MPV and the percentage of lymphocytes were lower in the group of synthetic cannabinoid users and the TLC, MCH, MC, RDW were higher compared to the control group. The findings suggest that chronic use of synthetic cannabinoids can lead to deterioration of hematopoietic cells. Thus, recovery of subclinical haematological parameters should be considered in cannabis use disorder patients. The health impact of cannabis-induced immunomodulation is still unclear and additional studies are needed in this area.

Opioids

Haematological parameters have been widely studied in population of opioid users. Most of these studies are cross-sectional in design. Literature reveals that chronic use of opioids alters the blood homeostasis via effects on the hematologic series [41]. Haghpanah, et al. [42] reported that heroin addicts had significantly increased neutrophil count (NEUn), Mean Corpuscular Volume (MCV), and Hematocrit (HCT), while they had a significant reduction in lymphocytes (LYMn) and mean corpuscular hemoglobin concentration (MCHC It is also observed that they have an increase in terms of mean platelet volume (MPV) [41]. Furthermore, decrease in RBC lead to increase in MCV, hemoglobin (HGB), HCT, Red Distribution Width (RDW) compared to the healthy individuals [43]. It has been found in some studies that haemoglobin, haematocrit, and platelet count were comparable in a group of opioid users and a group of healthy controls [44]. However, there was no difference in the parameters of people who were enrolled

in methadone maintenance programs when compared with those who were not in maintenance treatment programs. Another study, with a larger sample of 180 males who were referred for a 3 month treatment program, examined the haematological parameters of people who were dependent on heroin or opium for at least a period of two years and those who abstained for at least a period of 1 month [42]. The results showed no difference in the RBC among the groups of dependent, withdrawal or control population. The WBC was significantly increased in the dependent group compared to the controls. The neutrophil and monocyte counts showed a significant reduction whereas the lymphocyte count was significantly increased in the opioid dependent group compared to the controls. Haematocrit level in the dependent group was increased in comparison to the other two groups. An aspect of opioids that is clinically relevant is their effect on the immunity-related cells. Most of the published studies have suggested that opiates are involved in the regulation of cell-mediated immune responses in heroin addicts [45]. Moreover, long-term use of opioids leads alternations in both innate-adaptive immune systems and other diagnostic hematologic cells. It has also been reported that heroin dependence also effects some major elements as well as trace elements (zinc, manganese, iron, copper, and bromine) [46]. Among these elements, iron has significant effect on tissue oxygenation and on cognitive functions. The change in concentrations of iron may disrupt the blood cell physiology, especially the erythrocyte series [47]. Literature reveals that opioids differ in their effects depending on their receptor-specificity and the duration of use [48]. Animal studies have shown that morphine when chronically administered increases the numbers of regulatory T cells and also functioning of Th17 cells [49]. Endogenous opioid ligands, such as Met-enkephalins have been found in some studies to increase the population of CD4+ vet T cells, however, other studies have found that they inhibit the activity of these cells [50]. B cells functioning in terms of mitogenic response to bacterial infections is affected by morphine, however, there does not seem to be appreciable change in the number of these cells [48]. A study from Northern India that examined ahematological parameters in a population of 63 treatment-seeking injecting drug users found that the haemoglobin concentration ranged from 7.5 and 13.5 g/dL, ESR was abnormally increased in two-thirds of the sample and DLC showed abnormalities in 39.7% of the sample [51]. These findings suggest that changes in haematological parameters occur among opioid drug users.

Cocaine

Cocaine is known to have vasoconstrictor effects in humans. Cocaine administration has been shown to increase the Hb level, RBC count and haematocrit through its transient effect of causing splenic constriction [52]. However, there were no changes in the WBC or platelet count. These findings were replicated in a study that examined effects of intra-nasally snorted and intravenous cocaine administration [53]. Contrary findings were seen in a study that examined the nutritional status of crack cocaine users in Brazil [54]. The study found that the haematocrit level was less than normal in 36.4% of the sample and haemoglobin was less than normal in 32.4%. This study had the limitation that the use of other substances, including alcohol, was not an exclusion criterion.

Inhalants

Inhalant abuse is on rise and is a serious drug problem worldwide, particularly in disadvantaged populations and among adolescents. Inhalants are volatile substances that produce chemical vapours that can be inhaled intentionally to induce a psychoactive, or mind-altering euphoric state. These substances have the potential to cause major physiological and neurological damage. The substances inhaled are often common household products that contain volatile solvents correction fluid, adhesive, paint thinner and nail polish remover. Some of the volatile substances in these products include toluene, chloroform, propane, acetone and many halogenated hydrocarbons. The diagnosis of inhalant abuse relies almost entirely on a thorough history and a high index of suspicion [55,56]. No specific laboratory tests confirm solvent inhalation. For inhalant intoxication treatment is generally supportive, because there are no reversal agents. Available research reports suggest that inhalant use may be associated with substantial haematological, renal, hepatic, and neurological morbidity and mortality [57-59]. Adverse effects of inhalants include aplastic anemia, bone marrow suppression, and leukaemia are among the haematological [57]. Long-term inhalant use can cause bone marrow suppression, leading to leukopenia, anemia, thrombocytopenia, and hemolysis [58,59]. Study from Turkey evaluated the haematological and biochemical changes in inhalant-abusing adolescents living in Istanbul, Turkey [60]. The findings showed no significant relation between volatile abuse and haematological parameters. Published research from India shows low hemoglobin in 25% of inhalant users. Neutrophils, lymphocytes, eosinophils, and monocytes were elevated beyond normal in 10.8%, 6.5%, 15.2%, and 7.5%, respectively. There was no evidence of leukopenia. The study adds to the limited date available on the treatment-seeking inhalant users from Indian settings and additional studies need to done to examine the pattern of inhalant use in larger samples, across multiple sites in a prospective manner [61].

Conclusion

Numerous clinical observations support the notion that substance abusers do show some haematologi-

cal abnormalities (e.g., haemoglobin, white blood cells count, mean corpuscular volume, mean corpuscular haemoglobin concentration, red blood cells count, hematocrit) and that can lead to host tissues organ dysfunction. Routine haematology investigations may be beneficial for defining the homeostasis condition of the body, which may suggest to treatment approaches. There is a need to carry out further research work on various haematological and other health-related effects associated with illicit substance abuse. This may lead to a better understanding of the haematological effects in alcohol and substance abusers.

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