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Evaluation *of Some Haematological Parameters* Among Marijuana Smokers In Yenagoa, Nigeria.

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ABSTRACT:

The study investigated the effect of marijuana smoking on some haematological parameters of smokers in comparison to non-smokers. Blood samples were collected from one hundred and eighty nine randomly selected male voluntary marijuana smokers (test) and one hundred non-smokers (control) resident in Yenagoa, Nigeria. All subjects were between 18-50 years. The haematological parameters analysed include haemoglobin concentration (Hb), packed cell volume (PCV), total white cell count (WBC), red blood cell count (RBC), differential white cell count, platelet count (PLT); using Sysmex SX-1000i automated haematology analyser; erythrocyte sedimentation rate (ESR), using Westergren method; prothrombin time (PT) and activated partial thromboplastin time (APTT) using method adopted from Dacie and Lewis, 1994. There was no significant difference in the PCV, Hb, Total WBC, RBC, PT, APTT, PLT, monocyte count, and basophil count between the test subjects and the controls ($p>0.05$). But there was a significant decrease in neutrophil count in the test subjects when compared with the controls ($p<0.05$). Also, there was a significant increase in ESR, lymphocyte count and eosinophil count in the test subjects when compared with the controls ($p<0.05$). This study has shown that marijuana usage results in marked differences in some haematological parameters which may lead to inflammation, reduced immunity and ability to fight infections by the users.

Keywords: Evaluation, haematological parameters, cannabinoids.

INTRODUCTION:

Marijuana is a green, brown or gray mixture of dried shredded leaves, stems, seeds and flowers of the female *Cannabis sativa* plant. It is the most widely used illicit drug globally (Compton, *et al.*, 2005; Pyriyamvada, *et al.*, 2010). Its health and psychological effects are not well understood and remains the subject of much debate, with opinions on its risks polarized along the lines of proponents' views on what its legal status should be. An unfortunate consequence of this polarization of opinion has been the absence of any consensus on what health information the medical profession should give to patients who are users or potential users.

Marijuana contains over four hundred and twenty six (426) chemical entities and more than sixty (60) are of the cannabinoids class (Mahlberg, *et al.*, 2001) that includes cannabidiol (CBD) cannabinol (CBN) and delta-9,-tetrahydrocannabinol (THC) (Klein, *et al.,* 1998). Cannabinoids have been studied extensively in recent years and have been found to have important function in many physiological and pathophysiological processes. Marijuana cannabinoids are considered to be immunomodulatory that have the ability to increase or decrease immune function (Klein, *et al.*, 1998). Evidently, the major psychoactive compound in marijuana extracts is THC which produces a multiplicity of effects in humans (Adams and Martin, 1996; Cabral, *et al.*, 1998). Marijuana has a THC content of 0.5-5.0% (Adams and Martin, 1996). Marijuana is mostly smoked because this is the easiest way to achieve the desired psychoactive effects (Hall, *et al.*, 1994). The tar phase of marijuana smoke contains same carcinogenic compounds contained in tobacco smoke, including polycyclic hydrocarbons such as benz(a)pyrene which was identified as a key factor promoting human lung cancer (Denissenko, *et al.*, 1996), nitrosamines, reactive aldehyde and 50% higher concentration of polycyclic hydrocarbons which has been shown to promote mutations in the p53 oncogene believed to play an important role in human cancer (Denissenko, *et al.*, 1996).

The most beneficial use of marijuana is its antiemetic properties in patients who are receiving chemotherapy and its ability to reduce intraocular pressure in the treatment of glaucoma. It can be used for cancer patients, AIDS patients, and other chronic diseases to produce a sense of euphoria (Scully, 2007). Its effect on the user depends on its strength or potency which is related to the amount of delta-9-tetrahydrocannabinol (THC) it contains. It produces euphoria and relaxation, perceptual alterations, time distortion, intensification of ordinary sensory experiences, anxiety and panic reactions (Ranganathan, *et al.*, 2006; Osborne, *et al.*, 2008). Marijuana smoking increases heart rate by 20-50% (Hall, *et al.*, 1994). Concerns have been raised about the potential for long-term marijuana consumption to increase risk for schizophrenia, bipolar disorders and major depression (Leweke and Koethe, 2008; Rubin and Parolaro, 2008).

The discovery of cannabinoids receptors located throughout the brain and body, suggested that the use of marijuana affects the brain in the same manner as a naturally occurring brain chemical (Abadinsky, 2004). There are two types of cannabinoids receptors (CB1 and CB2) (Alexander *et al.*, 2009; Brady, *et al*., 2009). The CB1 receptor is found primarily in the brain, at the terminal of the central and peripheral neurons (Howell, *et al.*, 2002; Pertwee and Ross, 2002; Szabo and Schlicker, 2005). The CB2 receptor is most abundantly found on the cells of the immune system, including the spleen, thymus, tonsils, bone marrow, pancreas, splenic macrophages/monocytes, mast cells, and peripheral blood leukocytes (Bouaboula, 1993; Howlett, *et al.*, 2002; Fride, 2004; Delisi and Lynn, 2008).

The influence of marijuana on immune function has been examined extensively over the last 25years using experimental models involving drug-abusing human subjects and experimental animals exposed to marijuana smoke or injected with cannabinoids and invitro models employing immune cell cultures treated with various cannabinoids. For the most part, invivo and invitro studies suggest that marijuana (THC) is an immune modulator and has immunosuppressive effects on T and B lymphocytes (Kaminsky, *et al.*, 1996; Klein, *et al.*, 1991; Bhargava, 1996), as well as natural killer (NK) cells (Kusher, *et al.*, 1994; Klein, *et al.*, 1998), macrophages (Baldwin, *et al.*, 1997; Zheng, *et al.*, 1996; McCoy, *et al.*, 1995; McCoy, *et al.*, 1999), and neutrophils (Murikinati, *et al.*, 2010). THC may exert its immunosuppressive effects through disruption of there homeostatic mechanisms by inhibiting the ability of lymphocytes to produce type 1 cytokines and promoting type 2 cytokine production (Newton, *et al.*, 1994). In addition to studies examining marijuana effects on immune cell, other reports have documented that these substances modulate host resistance to various infectious agents. These results are intriguing and demonstrate that cannabinoids can be immunomodulatory and enhance the disease process (Klein, *et al.*, 1998). In addition to the haemodynamic effects, marijuana smoke is associated with an increase in carboxyhaemoglobin resulting in decreased oxygen carrying capacity (Hollister, 1986). Marijuana may increase factor v11 activity, however, there are mixed results in terms of the effects of smoked marijuana on platelet function (Heiden, *et al*., 1980). Thus taken together, smoking marijuana is associated with an increase in myocardial oxygen demand and a concomitant decrease in oxygen supply (Pearl and Choi, 1992).

Presently, there is an increase in the use of marijuana by young able-bodied Nigerians, cutting across sex divisions. Reasons proffered include frustrations, on account of current and consistent difficult economic situation in the country. The paucity of information on the haematological status of marijuana users in this part of the country, the importance on blood constituents individually or collectively, to healthy living and the reality of the poor status of our country's economy for some time to come, with the government not succeeding in alleviating the situation effectively all crystallize to form the basis of this study, which assessed the effect of marijuana usage on some haematological parameters in smokers in order to elucidate possible deviations from the non-smokers.

MATERIALS AND METHODS.

This study was carried out in Yenagoa, Bayelsa state South-South Nigeria. Bayelsa state is located within Latitude 4^0 15^1 North and Latitude 5^0 and 23^1 South. It is also within longitude 5^0 22^1 West and 6^0 45^1 East. It is bounded by Delta State on the North, Rivers State on the East and the Atlantic Ocean on the Western and Southern parts. Information on age, socio-economic status, lifestyle pattern such as consumption of alcohol, smoking and taking of medicines including past and present illnesses, were obtained by questionnaires. They were drawn from low, middle and high socio economic classes and of different ethnic groups.

SELECTION CRITERIA FOR SUBJECTS

Inclusion Criteria:

Subjects were 18years and above

Only subjects whose urine sample confirmed the presence of cannabinoids using ACRO BIOTECH diagnostics cannabis test strips were selected for this study.

Exclusion criteria

Subjects above 60years, those who refused consent, immunocompromised subjects, those who smoked both marijuana and cigarette and subjects with history of bleeding or clotting disorders were excluded from the study.

STUDY DESIGN

A completely randomized experimental design was used for this study. Evidence of marijuana smoking was confirmed at smoking joints where volunteers, certified by colleagues as smokers for at least two years were recruited. Informed consent was obtained from volunteers before commencement of the study. The study involved a "posttest only" randomised experiment. Control subjects were individuals who have never smoked marijuana or cigarette in their life time. Blood specimen of both marijuana smokers and non-smokers were collected randomly and analysed.

ETHICAL CONSIDERATION

Permission was obtained from the ethics committees of the Federal Medical Centre Yenagoa and the Bayelsa state ministry of Health, Yenagoa.

RESULTS

Two hundred and eighty nine persons participated in this study, comprising one hundred and eighty nine apparently healthy marijuana smokers and one hundred non-smokers representing the control group. All the subjects were between 18-50 years.

Table 4.1 is a comparison of the mean ± standard deviation haematological parameters between non-smokers (controls) and marijuana smokers (test subjects). There was no significant difference between the mean Total WBC, HB, PCV, RBC, PT, APTT, platelet count, Monocyte % and Basophil % of marijuana smokers and that of control subjects (P>0.05).

There was a significant difference between the mean, ESR, Neutrophil %, Lymphocyte % and Eosinophil % of marijuana smokers and that of controls (P<0.05).

Table 4.1: Comparison of Mean ± standard deviation Haematological Parameters between Control and Test Subjects.

Parameters	Control Samples	Test Samples	P Value	Inference
Total WBC Count ($x10^9$/L)	8.6± 0.88	6.1 ± 0.94	> 0.05	(NS)
Platelet ($x10^9$/L)	194±25.90	224 ±7.03	> 0.05	(NS)
RBC (x 10^{12}/L)	4.1 ± 0.42	5.7 ± 0.52	> 0.05	(NS)
PCV (%)	37.69 ± 3.52	40.61 ± 3.94	> 0.05	(NS)
Hb (g/dl)	12.43 ± 1.18	13.33 ± 1.25	> 0.05	(NS)
PT (secs)	13.17 ± 0.82	12.61 ± 1.84	> 0.05	(NS)
APTT (secs)	33.63 ± .61	33.64 ± 0.94	> 0.05	(NS)
ESR (mm/h)	4.28 ± 1.82	13.88 ± 5.36	< 0.05	(S)
Neutrophils (%)	66.09 ± .90	28.28 ± 2.53	< 0.05	(S)
Lymphocytes (%)	28.22 ±5.93	54.57 ± 2.88	< 0.05	(S)
Monocytes (%)	3.06 ± 1.02	5.88 ± 1.66	> 0.05	(NS)
Eosinophils (%)	2.33 ± 0.85	10.59 ± 2.99	< 0.05	(S)
Basophils (%)	0.30 ± 0.14	0.68 ± 0.20	> 0.05	(NS)

KEY: (NS) = Non significant (S) = Significant

DISCUSSION

This study has clearly demonstrated the effects of marijuana smoking on some haematological parameters of smokers and this cannot be overemphasized as there was a significant difference in some of the parameters between marijuana smokers at different marijuana years and that of the non-smokers. There is abundant evidence that haematological values vary considerably between this two study groups. These changes may be due to several factors. Reports from all over the world have been published on packed cell volume, haemoglobin concentration, red blood cell count, platelet count, total white cell count, differential white cell count, erythrocyte sedimentation rate, prothrombin time and activated partial thromboplastin time. So far, most of these findings involved the use of concentration of cannabinoids far in excess of those employed in social use of marijuana; hence it is necessary that similar data be made available so as to compare the parameters of those involved in the recreational use of marijuana.

In this study, the mean haemoglobin concentration obtained in marijuana smokers (test group) was marginally higher than those obtained in non-smokers (control group), but not statistically significant ($P>0.05$). Also the mean packed cell volume obtained in the test group was marginally higher than those obtained in the control group, but not statistically significant ($P>0.05$). This finding is similar to that of Oseni, *et al*., (2006); Amna and Nabiala (2011) but contrary to the findings of El-shahat, (2011) who got higher haemoglobin concentration and packed cell volume in the control group. There are many mechanisms by which marijuana smoking may raise the Hb concentration and PCV. Smoking leads to an appreciable rise in concentration of carboxyhaemoglobin which does not function in oxygen transport; an erythropoietin-mediated increase in erythropoiesis therefore occurs.

The red blood cell count obtained in the test group was also higher than those in the control group, but not statistically significant. This confirms the study by El-shahat, (2011) who obtained a higher red blood cell count in the test group. The non-significant difference in the haematological values between smokers and non-smokers of cannabis is in line with the report of Isager and Hagerup, (1971), who found no effect of pipe and cigar smoking on haematological values. It is also in agreement with Beacofield *et al*., (1973), that haemoglobin and PCV in the blood of ten native volunteers, who smoked cannabis containing 10 mg cannabinoid remained within the normal range. This result is further reinforced by the report of Beacofield *et al*., (1973) that there was no significant difference between smokers and non-smokers in chest x-ray, blood parameters and alveolar debris. The marginally higher value observed for PCV in marijuana smokers in this study, agrees with Isabell and Hagerup, (1971) on cigarette smokers where PCV was increased as a result of smoking. This was explained by the increase in carbon monoxide level in the blood of smokers which induced erythrocytosis (Tashkin *et al.,* 1972) which has been suggested to result in the intrathorasic airway obstruction or pulmonary insufficiency leading to ventilation/perfusion imbalance that results in functional hypoxia or hypoxaemia and arterial oxygen unsaturation; increasing the demand on bone marrow for RBC production observed as increased haemoglobin concentration to increase the oxygen carrying capacity of the blood (Rubin and Comitas, 1975). The authors added that the brief exposure to smoke from marijuana cigarettes stimulated the formation of reactive oxygen species (ROS) by 80% over control levels and lowered intracellular glutathione levels by 81%. Also, the smoke-induced ROS generation was in a dose- and time-dependent manner, suggesting that most of the oxidative effects are produced by the gaseous phase and concluded that Delta9-THC present in the smoke is a potent source of cellular oxidative stress that could also contribute significantly to cell injury and dysfunction in the lungs of smokers. Also, the findings of the work are in agreement with the research by Valk, *et al*., (1997), who reported that in vitro anandamide (at low micromolar concentrations) acted via cannabinoid CB2 receptors to synergize with colony-stimulating factors (CSFs), interleukin-3 and erythropoietin to stimulate haematopoiesis.

The total white cell count obtained in this study was marginally higher in the non-smokers than in the marijuana smokers, but not statistically significant ($P>0.05$). The variations observed were all in line with the reports of Klein, *et al*., (2003); Oseni, *et al*., 2006; El-shahat, (2011); but contrary to the finding by Amna and Nabiala (2011) who found no changes between smokers and non-smokers. The marginally lower value observed in total white cell count of smokers in this study, though within the normal range is in line with the report of Brent-Moore (2005) that induced peripheral blood leukopoenia was caused by a single oral dose of 23-30 mg of cannabinoid per kg weight in rats. Possible complications arising from additional inflammatory agent, which might complicate the bronchitis experienced generally in smokers, could thus be implicated with reduced total leukocyte count. In the present study, reduction of the count of total white blood cells in marijuana smokers

confirm the disturbances in the immune system function and the immune response to the smoke inhalation. This also accounted for the increase ESR observed in this study. Also, the findings of this study is reinforced by the report by Klein, *et al*., (2003) who found that a control group smoking a single marijuana cigarette every day for a year had a white-blood-cell count that was 39 percent lower than normal, thus damaging the immune system and making the user more susceptible to infection and sickness.

The significantly increased lymphocyte percent observed in this study agrees with the findings by Amna and Nabiala, (2011); El-shahat, (2011) but is contrary to the low lymphocyte count observed by Oseni, *et al*., (2006).

On the other hand, the mean neutrophil count in the control group was significantly higher than that of the test group ($P < 0.05$). These confirm the findings by Oseni, *et al*., (2006); Amna and Nabiala, (2011); Murikanati, *et al*., (2010); El-shahat, (2011); that marijuana smoking results in a reduction in neutrophil count. The mechanism of liver damage by the marijuana smoke, involves crossing biological membranes by the excessively formed peroxynitrite which diffuse one to two cell diameters as was described by Denicola, *et al*., (1998). The latter diffusion allows significant interactions with lipids, DNA, and proteins causing more organs damage which may include, liver, gonads and pituitary glands (Hogg and Kalyanaraman, 1999 and Pryor and Squadrito, 1995). Sarafian, *et al*. (1999) showed that marijuana (MJ) smoking produces inflammation, edema, and cell injury in the tracheobronchial mucosa of smokers and may be a risk factor for lung cancer via oxidative stress mediated mechanism. Hepatic ischemia/reperfusion injury is a significant clinical problem involved in the liver failure associated with marijuana smoke which is mostly metabolized in the liver cells. Such injury is characterized by Kupffer cell activation and PMN cell infiltration and activation as well as inflammatory cytokine responses. The first step in the pathophysiology of this injury is the priming and recruitment of neutrophils into the liver vasculature upon reperfusion by inflammatory mediators. After recruitment of neutrophils into the liver vasculature, the second step comprises endothelial cell activation, which promotes the attachment and activation of inflammatory cells resulting in endothelial damage and liver dysfunction. Next, adherent inflammatory cells transmigrate through the damaged endothelium, attach to hepatocytes, and become fully activated to release oxidants, pro inflammatory cytokines, free radicals and large amounts of nitric oxide and proteolytic enzymes, which in turn trigger intracellular oxidative stress and mitochondrial dysfunction in hepatocytes, eventually culminating in cell death (Pacher, *et al*., 2007). The results of the present study confirm the conclusion of Hézode, *et al.,* (2005) who showed that daily cannabis smoking is significantly associated with fibrosis. The mechanism of the latter liver damage may involve activation of CB1 receptors as was shown by Tam, *et al*. (2011) who illustrated that such receptors is activated in various liver diseases and contributes to the underlying pathologies. Also, the reduction of the number of the neutrophils caused by cannabinoids was reported in previous studies by Murikinati, *et al*. (2010) who suggested that the activation of cannabinoid 2 receptor (CB2) reduced ischemic injury and this action involved the reduction of the number of neutrophils in the ischemic brain of experimental mice. Also phagocytosis impaired in animals exposed to acute marijuana smoke was due to a water soluble cytotoxin in the gas phase of fresh smoke possibly impairing glycolysis necessary for some of the cell energy for phagocytosis (Huber, *et al*., 1980). Daniel and Watson (1987) reported that phagocytic activity inhibition may be due to the effect of cannabis on bone marrow synthesis and maturation of neutrophil cells.

Alcohol and Drug Education (2006) that marijuana use can weaken the immune system and interrupt maturation of white blood cells. Therefore, marijuana users may be more vulnerable to illness

The occurrence of higher eosinophil count in smokers, while the values in all non-smokers studied were normal, can be explained by the observation of Brent-Moore *et al*. (2005) that cannabis plants are contaminated with a range of fungal spore organisms, which cause secondary eosinophilic pneumonia. According to Rubin and Faber (1998), apart from circulating in the blood, eosinophils are also found in tissues near points of external environmental contact and in inflammatory cellular infiltrates. They exhibit specialized function in certain disorders and are conspicuously active in their protection against foreign substances like smoke and cannabinoids. The eosinophilia manifestation in the marijuana smokers could be as a result of individual response since susceptibility is individual dependent. Such individual resistance could be on account of nutritional status as well as dose and chronicity effect.

Also the findings of this study which showed a slight increase in platelet count in smokers is in agreement with the work of Erikssen, *et al*., (1994) who observed a small but statistically highly significant increase in platelet

count in marijuana smokers. This study also showed a slightly decreased prothrombin time and activated partial thromboplastin time among marijuana smokers when compared with non-smokers. The decrease, though not statistically significant ($p>0.05$) was in agreement with the work of Coetzee, *et al*., (2007), that Cannabis sativa and the cannabinoids, THC and CBN, display anticoagulant activity and may be useful in the treatment of diseases such as type 2 diabetes in which a hypercoagulable state exists.

CONCLUSION:

Some haematological characteristics of marijuana smokers differ significantly from non-smokers. The most likely consequences are easy predispositions of cannabis smokers to preventable infections, consequent upon the possibility of reduced humoral and cell mediated immune responses. The occurrence of significantly higher eosinophil counts in the test subjects suggests an inflammatory, allergic reaction consequent upon the precipitated eosinophilia conspicuous in these subjects. This also reflected in the increase in other inflammatory marker such as erythrocyte sedimentation rate as was observed in the study. In addition to recruiting and activating other cells of the immune system, neutrophils play a key role in the front-line defense against invading pathogens. Neutrophils also release an assortment of proteins in three types of granules by a process called degranulation. The contents of these granules have antimicrobial properties, and help combat infection. Therefore, neutropenia makes an individual highly susceptible to infections.

Furthermore, the slight decrease in prothrombin time in marijuana users is as a result of increased factor vii activity associated with heavy use of marijuana. This study has shown that heavy marijuana usage results in marked differences in some haematological and immunological parameters which may lead to reduced immunity and ability to fight infections by the users. It is also being recommended that further studies be carried out to check the therapeutic use of marijuana in the treatment of diseases in which hypercoagulable states exist

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