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Neutrophil to Lymphocyte ratio of Synthetic Cannabinoid Intoxication

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ABSTRACT

Synthetic cannabinoids represent an increasingly popular trend, and acute intoxication is widely seen in emergency rooms and intensive care units (ICU), as they are inexpensive and easily accessible. Cannabinoids mediate their effects through binding specific receptors which are members of the G protein coupled receptor superfamily. Cannabinoid-2 receptors are primarily found in the immune system and mediate immunosuppression by inducing apoptosis, inhibition of proliferation and suppression of cytokine and chemokine production. Many studies have discussed the effects of cannabinoids on the hematological and immune systems but controversial results have been reported. The aim of this study was to identify laboratory findings of acute synthetic cannabinoid intoxication. Forty-two patients, admitted to the 'Anesthesia intensive care unit' between 2014 and 2015 with synthetic cannabinoid intoxication, were studied retrospectively to assess the relationship between synthetic cannabinoid intoxication and complete blood count (white blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils) and neutrophil to lymphocyte ratio. WBC neutrophil count decreased at ICU discharge when compared to ICU admission ($p<0.001$). The ratio of neutrophils to lymphocytes was also lower at ICU discharge when compared to ICU admission ($p<0.05$).

Key words: synthetic cannabinoids, intoxication, neutrophil to lymphocyte ratio

INTRODUCTION

Synthetic cannabinoids represent an increasingly popular trend, and acute intoxication is widely seen in emergency rooms (ER) and intensive care units (ICU), as they are inexpensive and easily accessible. Use of synthetic cannabinoids has psychiatric, medical, and social consequences. They are found in powder form or loose leaf form. Powder form may be dissolved and sprayed onto a dried herbal substrate and packed, or purchased as a pre-rolled product. Various flavors may be added and they may contain different synthetic cannabinoids as well as preservatives, additives, amides, esters and benzodiazepines. These products are sold on the streets and they are typically smoked in cigarette papers or cannabis pipes. (1) Some of these products are marketed under different names and forms from head shops (a head shop is a retail outlet specializing in equipment used for consumption of cannabis and tobacco and items related to cannabis culture and related countercultures; products may include magazines (e.g., about cannabis culture, cannabis cultivation, tattooing and music) and gas stations). Ingredients change over time to avoid legislation. When a compound is banned, it is replaced by a pharmacologically similar compound to avoid regulations. (2) Thus, it can cause different clinical findings, depending on the ingredients.

Phytocannabinoids, or plant-derived cannabinoids, include delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis. Cannabinoids mediate their effects through binding specific receptors which are members of the G protein coupled receptor superfamily. To date, two cannabinoid receptors have been identified: Cannabinoid-1 receptors (CB1) and Cannabinoid-2 receptors (CB2). CB1 are expressed primarily in the central nervous system (CNS) and are responsible for the psychoactive effects of cannabinoids by modulating neurotransmitter release. In contrast, CB2 are localized primarily in immune cells such as lymphocytes, macrophages and neutrophils and are responsible for immunomodulatory effects of cannabinoids. (1,3,4) While THC is a low-efficacy partial agonist of cannabinoid receptors, the synthetic cannabinoids are high-potency full agonists for CB1 receptors. (5)

Most synthetic cannabinoids are not currently found using routine toxicology screening as they contain synthetic cannabinoids from different chemical classes. Some synthetic cannabinoids can be measured in the serum using chromatographic methods with mass spectrometry but these tests cannot be performed in many hospitals and they are time consuming and expensive. (1,6) Single use of THC can be detected up to 3 days while daily use can be detected up to 10 days. (6)

While many of the acute effects are similar to the effects of cannabis, these effects may differ clinically in terms of intensity and it is unclear whether they are related to the differences between synthetic cannabinoids and THC or to the noncannabinoid components. (1) These effects include mood disorders (euphoria, negative mood), anxiety, psychosis, cognitive and

neurological function disorders (dizziness, seizures, tremor, ataxia). Cardiovascular effects include tachycardia, bradycardia, ECG changes, and arrhythmias. Synthetic cannabinoids also induce dry mouth, reddened conjunctiva, pupillary changes including miosis and mydriasis, blurry vision and light sensitivity. In addition to psychiatric and physical symptoms, a number of acute changes in laboratory parameters have been reported in individuals who have intoxication. Hyperglycemia, hypokalemia, elevated creatinine, acidosis, elevated phosphokinase and elevated white blood cell count are reported. (1,7)

Many recent studies have indicated that the neutrophil to lymphocyte ratio (NLR) is a significant inflammatory marker in diagnosis of various diseases such as pulmonary thromboembolism, (8) malignancy, (9) cardiovascular (10) and inflammatory diseases. (11) It is also an inexpensive inflammatory marker that provides quick results. In this study we aimed to identify laboratory findings of acute synthetic cannabinoid intoxication and to assess the relationship between synthetic cannabinoid intoxication and NLR.

MATERIAL AND METHODS

A total of 56 patients admitted to the ICU between 2014 and 2015 with synthetic cannabinoid intoxication were studied retrospectively after approval by the local ethics committee. Synthetic cannabinoid intoxication information was obtained by witnesses or evidence such as loose leaf forms or rolled cigarettes found with the patient. All patients included in the study had used synthetic cannabinoids with inhalation and smoking, no ingestion case was reported. Forty-two patients, with laboratory results from admission to ER and discharge from ICU, were included in our study, whereas patients with missing data and with concomitant alcohol use (with blood ethanol levels more than 50 mg/dL) were excluded. Laboratory results of complete blood count (WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) duration of ICU stay, age, and intubation data were recorded. Neutrophil Lymphocyte Ratio was calculated both on admission and discharge. Leukocytosis was defined as a WBC >10.5×103cells/μL and leukopenia was defined as WBC count < 4.0×103 cells/μL. Received data was analyzed with SPSS 15.0. Continuous variables were represented as mean ± SD. Appropriateness of the variables to a normal distribution was analyzed with Kolmogorov-Smirnov test. Data were compared with paired T Test. A $p< 0.05$ was deemed statistically significant.

RESULTS

A total of 42 patients were included in the study. All patients were male and aged between 21-28 (22 ± 1.6) (mean±SD) years of age. Mean ICU duration was 1.66 ± 0.4 days. All patients had neurocognitive disorders, 4 patients (9.5%) had respiratory disorders that needed intubation and mechanical ventilation. Laboratory tests at both admission and discharge were compared statistically. 24 patients (57%) had leukocytosis and none of them had leukopenia on ER admission, and only 7 (16%) patients had leukocytosis on discharge. WBC and neutrophil count decreased at ICU discharge when compared to ICU admission ($p<0.001$) (table 1). NLR was found to be 5.5 ± 4.7 on admission and 2.7 ± 2.2 on ICU discharge (table 1). The NLR was also decreased on ICU discharge when compared to ICU admission ($p<0.05$) (table 1).

Table 1. Comparison of data between intensive care unit (ICU) admission and discharge.

	ICU admission	ICU discharge	p
WBC	11.7 ± 4.0	8.7 ± 2.7	<0.001
Neutrophil	8.7 ± 4.0	5.5 ± 2.8	<0.001
Lymphocyte	2.11 ± 1.01	2.35 ± 0.57	0.161
Monocyte	0.71 ± 0.40	0.65 ± 0.26	0.305
Eosinophil	0.11 ± 0.11	0.15 ± 0.11	0.110
Basophil	0.04 ± 0.03	0.03 ± 0.04	0.782
Platelet	229.7 ± 73.5	215.7 ± 53.3	0.94
NLR	5.5 ± 4.7	2.7 ± 2.2	0.01

NLR, Neutrophil to lymphocyte ratio; WBC, White blood cells.

DISCUSSION

Cannabinoids are a group of compounds that mediate their effects through cannabinoid receptors CB1 and CB2, which are G protein coupled receptors found on immune system cells. While CB1 is expressed in the CNS and plays a role in modulating GABA and glutamate neurotransmission, CB2 is primarily found in the immune system and mediates immunosuppression by inducing apoptosis, inhibition of proliferation and suppression of cytokine and chemokine production. (12-14) THC is the major active ingredient in marijuana which is a low efficiency partial agonist of cannabinoid receptors. Synthetic cannabinoids are high efficiency full agonists of CB thus consequences of synthetic cannabinoid use differs from marijuana-like effects. Also some synthetic cannabinoids have long half-lives as a result of active metabolites. (1,14)

The neutrophil to lymphocyte ratio has been widely used in identifying the degree of inflammation, as white blood cell count and its subtypes play an important role in inflammatory processes. NLR is claimed to be more useful as it is a combination

of two independent inflammatory markers. (15,16) However, no studies have been found regarding NLR in acute synthetic cannabinoid intoxication.

Many studies have discussed the effects of cannabinoids on the hematological and immune system but controversial results have been reported. Oseni at al. studied the effects of marijuana smoking on some hematological parameters, including WBC, hemoglobin, platelets and NLR, and found no significant difference with non-smokers in contrast to our study. (16) However they included smokers that used marijuana for at least two years which differs from our study population, as inexperienced smokers had symptoms of dizziness, tachycardia, tremor and disorientation while experienced users did not.

Altınısık et al. reported a series of synthetic cannabinoid intoxication cases, followed up in ICU, with leukocytosis in 33%, and leukopenia in 8% of cases. (7) However they mainly focused on clinical presentation of intoxication. In our study 24 patients (57%) had leukocytosis and none of them had leukopenia on ER admission, and only 7 (16%) patients had leukocytosis on discharge.

Mukhtar et al. reported a decrease in total WBC count and neutrophil count in rats treated with intramuscular cannabinoid extract administration compared to the control group. Another animal study by Obembe et al. reported a decrease in total WBC in groups fed different doses of cannabis sativa solution. Authors attributed the results to bone narrow supression which disturbs maturation of monocytes, as the design of these studies aimed at effects of chronic use. (17,18)

Limitations of our study include the relatively small sample size and our retrospective study design. Also we could not determine or obtain any information about the type of synthetic cannabinoid used, which may have affected our results. We also did not know if the patient was a chronic user of synthetic cannabinoids, other drugs or cannabis, which may have affected our results. As we focused on acute intoxication of synthetic cannabinoids, we compared WBC and NLR of patients admitted to ICU with an altered level of consciousness, with their control blood samples taken at discharge. Our study would be more valuable if we had obtained follow up results over a larger time interval.

CONCLUSIONS

Neutrophil count and neutrophil to lymphocyte ratio were decreased in discharge blood samples indicating hematological characteristics of synthetic cannabinoid intoxication. Cannabinoids have a potential use as anti-inflammatory agents against inflammatory and autoimmune diseases as well as for, treating sepsis. However synthetic cannabinoids differ from cannabinoids with their high potency and full agonist properties and therefore further studies should be performed on this subject.

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