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A RECENT NEW DISASTER IN INTENSIVE CARE UNITS: SYNTHETIC CANNABINOID INTOXICATIONS

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ABSTRACT

Background: We aimed to evaluate the clinical presentation and hospital course of patients admitted to the intensive care unit with synthetic cannabinoid intoxication. **Materials and Methods:** We performed a retrospective review of medical records of all patients admitted from January 2010 to December 2017 at Kartal Dr. Lutfi Kirdar Education and Research Hospital general intensive care unit in Istanbul, Turkey with synthetic cannabinoid exposure. **Results:** 31 patients (30 males, 1 female) were treated with synthetic cannabinoid intoxication and the median age was 28.4±12.3. The most common findings in the patients were discomfort (n=17 case, 54.8%) and the most frequent laboratory findings were leucocytosis (n=13 case, 41.9%). 10 patients (32.2%) required mechanical ventilation, 14 patients (45.1%), required vasopressors, and 2 patients (6,4%) needed dialysis. 28 patients (90.4%) were discharged and 3 patients (9.6%) died. **Conclusion:** Synthetic cannabinoid intoxication, has no specific treatment. The treatment should be symptomatic and should be planned according to the developing complication in these cases. We should consider the use of synthetic cannabinoid in differential diagnosis and the symptomatic treatment should be started early in intensive care unit.

Keywords: intensive care unit, synthetic cannabinoid, intoxication.

INTRODUCTION

"1-naphthalenyl methanone" which is called as "Bonsai" in Turkey is a narcotic agent containing synthetic cannabinoid (SC) and it is provided illegally **(1)**. SC is a type of drug that is produced synthetically on various plants in a laboratory environment, resulting in spraying and drying of strong, safety-indexed narrow chemical substances **(2)**. The sale of SCs over the internet sales sites started from the beginning of 2000s and has risen substantially worldwide **(3)**. The tendency of SC abuse is increasing in Turkey year by year because of its features, including its easy accessibility than narcotic drug, cheap price, and routine urine drug immunoassays do not detect the substance **(4)**. Serious adverse effects and significant organ dysfunction are observed clinically. We aimed to evaluate the cases with SC intoxication cases of the intensive care unit retrospectively according to demographic features, laboratory findings, treatment, complications, and prognosis.

MATERIALS AND METHODS

We evaluated retrospectively 31SC intoxication cases of the intensive care unit of Kartal Dr. Lutfi Kirdar Training and Research Hospital between January 2010 and January 2017. The medical record of ICU were the primary source of information for data collection.

Kartal Dr.Lutfi Kirdar Training and Research Hospital is tertiary care hospital containing600 beds with a multidisciplinary 32 general medicine and general surgery adult ICU beds. Because of the retrospective nature of this study, we waived the informed consent. Patients were enrolled in the study if the diagnosis of the SC intoxication was maintained by confirmation of the use of the agent by the patient or their relatives.

We excluded the patients who died before ICU admission and the patients who were transferred from the ICUs of other hospitals.

We evaluated the age, gender, the medications, hemodynamic parameters, laboratory findings as total blood count, blood glucose, liver function tests, renal function tests, serum electrolytes (sodium, potassium, chlorine, calcium). Indications for admission to intensive care, Glasgow Coma Score(GCS), APACHE (Acute Physiology and Chronic Health Evaluation) II **(5)** score was calculated using laboratory values obtained within 24 hours of ICU admission, chest graphies, ECGs, blood gas values, applied treatment modalities, inotropic support, lenght of ICU stay, duration of mechanical ventilation in intubated patients and complications observed in these patients were also examined.

Statistical analysis was made with the Statistical Package for Social Sciences (SPSS) software, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were given as numbers and percentages for categorical variables or as the mean ± standard deviation and median (minimum-maximum) for numeric variables.

RESULTS

During the study period, 3,591 patients were admitted to the ICU, and 31(30 male, 1 female) of them were SC intoxication (0.86%). Mean age was 28.4±12.3 years and the youngest were 16-year-old children, and most of the patients (96.7%) were male. All patients were using this substance by inhalation in cigarette form. GCS was >13 in 3(9.6%)patients, 10-13 in 12(38.7%) patients, 12 in 5(16.1%) patients, 12-9 in 5(16.1%) patients, 9> in 5 patients(Table 1).

In the intensive care unit, the mean duration of hospitalization was 8±3.16 days(4 days-13 days) and the mean APACHE II score at admission was 11,3±4,41(9-19).

In physical examination, the main cause of admission of the patients (n=10; 32, 2%) were altered mental status with unresponsiveness. Five (16.1%) unconscious patients with respiratory depression were required artificial ventilatory support in the ICU. Adequate self-respiration started after about 12-14 hours in these patients and they were extubated on the 2nd - 8th day of hospitalization. The mean duration of mechanical ventilation was 4±2.71 day. Other patients were followed in the room air in spontaneous breathing.

Six of the patients (19.3%) had a tonic-clonic seizure. In cardiovascular system examinations, tachycardia in 12 patients(38.7%), bradycardia in 3 patients (9.6%), supraventricular tachycardia in 2 patients (6.4%), severe hypertension in 2 patients (6.4%) were observed. In one patient (3.2%) ECG showed acute ST elevation and acute anterior myocardial infarction in one patient and percutaneous intervention was performed for this patient.

Mean arterial pressures, respiratory rate, SpO2, mean pulse rate, haemodynamic findings and laboratory values at admission to intensive care unit are shown in Table 2. In laboratory findings, leukocytosis in 13 patients (41.9%), elevation in hepatic function tests in 6 patients (19.3%), hyperglycaemia in 5 patients (16.1%), hypoglycemia in 5 patients (16.1%), hypocalcemia in 3 patients (9.6%), significant increase in renal function tests in 4 patients (12.9%) were observed. The respiratory acidosis was seen in the arterial blood gas in 7 patients (22.5%), and the mean lactate value was detected as 9±3.8 L/mmol

(2.6 mmol/L-28 mmol/L). In evaluating the mean laboratory values of the cases; hemoglobin: 10.18±2.8 mg/dl, AST:78.4±18.5 IU/L (161 IU/L-57012 IU/L), ALT: 83.6±111.2 IU/L (177 IU/L-61348 IU/L), LDL: 1015±115IU/L (1245 IU/L-10120 IU/L), bilirubin: 1.4±1.5 mg/dL (07-2.3 mg/dL), creatinine: 1.2±1.2 mg/L (1.1-5.9 mg/L), leucocyte(/mm3): 4900±500/mm3, platelets: 83.550±62.500/mm3 (27000/mm3-65000/mm3) was found. The laboratory values of the patients in the intensive care unit are shown in Table 2.

Five patients (16.1%) were treated with inotropic drugs due to refractory hypotension and two patients (6.4%) underwent hemodiafiltration due to acute renal failure in the first 48 hours. During the ICU treatment, Twenty-eight patients (90.3%) were discharged to the ward and three patients (9.6%) died. The causes of death were sepsis, anoxic encephalopathy, and ARDS.

DISCUSSION

In this retrospective study; wedescribed the prevalence and management of SC intoxications in our intensive care unit between January 2010 to December 2017. Bonsai; is a herbal mixture obtained by combining SCs in different proportions. It is difficult to predict clinical effects due to the presence of SCs in different combinations and proportions in mixtures sold in today's market. Due to the variability in content; their toxicity or adverse effects and their mechanism of action is variable **(6)**. Psychoactive effects of SCs are known as euphoria, psychosis, and changes in cognitive skills. Acute physical effects are defined as sweating, nausea, vomiting, appetite changes, hypertension/hypotension, chest pain, tachycardia, bradycardia, respiratory depression **(7)**.

The solution containing one or more SCs is added to the plant material (balm, peppermint, thyme, sage) by wetting or spraying, and is well preserved on the active substance **(8)**. Generally, dried leaves are used by smoking (pipe, water pipe) or by burning with smoke and withdrawing by inhalation **(9)**.

The main psychoactive component of SC, Δ9-tetrahydrocannabinol, exerts its effect on the cannabinoid receptors in the body by potent and prolonged activation **(10)**. The exact mechanism of SC toxicity is unknown. SCs elicit their effects via CB_1 and CB_2 receptors, which are part of the endocannabinoid system. These are also known subgroups of cannabinoid receptors: CB1 receptors are located in the central nervous system, cortical, subcortical regions, spinal cord dorsal root ganglia, and peripheral nerve regions with painful sensations. When these are activated, there is an impression of exaggeration, anxiety, panic, euphoria, psychosis, emotional, visual and auditory perception. CB2 receptors are peripheral and are found mostly in the immune system which are thought to cause immunosuppression **(11)**. The endocannabinoid system is very complex, and research is still ongoing and necessary for a continued understanding of its function **(12)**.

SCs are highly active and affects full agonists and receptors. For this reason, intoxication is associated with unexpected and significant toxicity. The use of SCs has been associated with the following symptoms: euphoria, sensory relaxation, subjective slowing in time, tachycardia, systolic hypertension, postural hypotension, anxiety, agitation, paranoid thoughts, depression, tachycardia, respiratory depression, confusion, seizure, psychomotor agitation, somnolence and these side effects are fatal **(13)**. We should monitor all cases with the affection of two or more organ systems and requiring mechanical ventilator support in intensive care unit **(14)**.

Hu et al. reported that 53% of those using synthetic cannabinoids were male and the average age was 20.6 **(15)**. Even when we work in a manner similar to the work done, the average age of the patients was 20.1 **(16-25)** similar to the previous studies **(16)**. The number of male patients was significantly higher than that of female patients and all cases used SCs in cigarette form.

Although there is insufficient information on the effect of respiratory depression, it is thought that it may be caused by the effects on the central nervous system and recent reports confirm that SC use alone

can result in cardiovascular complications. In our study; five (16.1%) unconscious patients with respiratory depression were treated with ventialatory support and all were extubated between 2 and 8 days. Mc Keeveret. al reported that the cardiovascular effects of cannabis are due to its effect on the autonomic nervous system **(17)**. In five patients (16.1%) refractory hypotension was treated with inotropic drugs.

We can conclude that the cardiovascular toxicity of SCs has relation with the patient's age, the presence of coronary artery disease, and the dose and type of synthetic cannabinoid ingested. The most common effect of synthetic cannabinoids is the increased heart rate **(18)**. It may cause supply-demand mismatch in myocard and as a result, premature ventricular contraction, Brugada-like ST segment abnormalities, sinus bradycardia, ventricular tachycardia, atrial fibrillation, sinus bradycardia with severe hypotension, myocardial infarction, and we may observe stroke and sudden cardiac death after synthetic cannabinoids use **(19)**.

Epileptic seizures associated with SCs are usually generalized tonic-clonic seizures andshould be treated with benzodiazepines with adequate sedation and airway management. In young male patients who have had seizures for the first time in first referral to emergency care unit, SC intoxication should be considered in the differential diagnosis **(20)**.

GCS was >13 in 3(9.6%) patients, 10-13 in 12(38.7%) patients, 12 in 5(16.1%) patients, 12-9 in 5(16.1%) patients, 9> in 5 patients. The APACHE II score was originally developed to assess the degree of organ dysfunction and severity in patients. APACHE II scores upon ICU arrival and mean APACHE II scores of the dead and discharged patients were similar 24.0 (20–27) and 25.0(20–27) respectively.

Treatment of SC intoxication usually consists of supportive and symptomatic care, but some patients may require longer observation and requiring more aggressive support. We must consider fluid replacement, monitoring of heart rhythm and vital parameters in initial management, arterial blood gas should be obtained, and serum electrolyte level should also be measured. Ventilatory support is required for respriatory failure **(21)**.

SC may cause acute renal failure due to acute tubular necrosis **(22)** and hepatocellular necrosis and hepatic failure **(23)**. Administration of intravenous fluids is helpful for associated rhabdomyolysis. In our cases; rhabdomyolysis occured but the patient died although hemofiltration was performed. Totally; 28 patients discharged, 3 patients died due to anoxic brain injury, sepsis and renal failure due to rhabdomyolysis.

Although we have no specific antidote to synthetic cannabinoids, in cases with intensive care unit demand, decontamination has limited effect. Intoxication can be expected to occur with ingested edible products and with SCs.

CONCLUSION

Patients are often brought to the emergency departments with unconsciousness. The use of SC has become especially prevalent among young adult males. Increasing diversity in the drug trade today has led to an increase in the market for new psychoactive substances.

The literature in this field is limited, and further research is needed to better understand SCs and their wide array of signs and symptoms, as consensus management guidelines for these cases remains elusive. In patients with negative drug panel despite the intoxication findings, we should consider the suspicion of the use of SC in the differantial diagnosis and we must start symptomatic treatment at an early stage.

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TABLES

Figure 1. Age distribution of the patients referred to ICU.

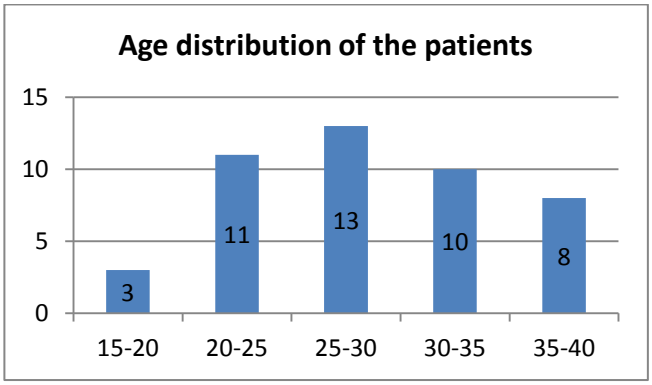

Figure 2. APACHE II scores of the patients referred to ICU.

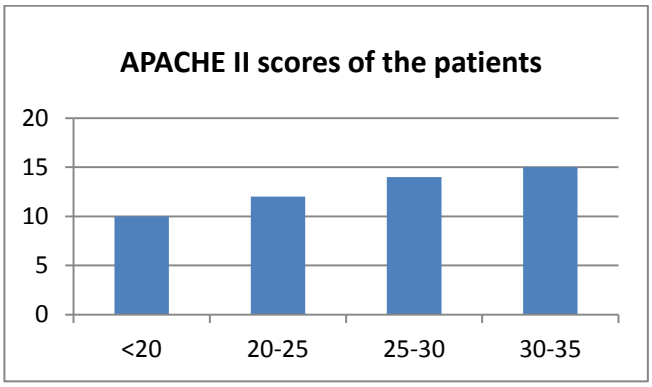

Table1. Age, gender, GCS, APACHE II hospitalization days, duration of mechanical ventilation and outcome of the patients

Characteristics	Total (n= 31, %)
Age (years), mean ± SD	28.4 ± 12.3
Gender, n %	
Male	30, 96.7%
Female	1, 3.2%
GCS, mean ± SD	8.43±4.14
APACHE II score, at admission, mean ± SD	27.0±1
ICU length of stay (day), mean ± SD	5.61±2.35
Lenght of mechanical ventilation (day), mean ± SD	5.3±2.71
Outcome, n, %	
Discharge	28, 90.3%
Exitus	3, 9.6%

Values are presented as median with interquartile range or number (percent).GCS: Glasgow Coma Score, APACHE II: Acute Physiology and Chronic Health Evaluation II, ICU: intensive care unit.

Table 2. The mean laboratory values of the cases

Values	Mean ± SD
Systolic blood pressure (mmHg)	134±67.9
Diastolic blood pressure (mmHg)	98±52.2
Breathing rate(/ minute)	16±3.3
Body temperature(C)	37.8±1.2
Heart rate (beat/ minute)	89.5±27.17
Sodium (mEq/L)	146±2.3
Potassium (mEq/L)	3.7±3.1
Urea (mg/dl)	34±11
Creatinine (mg/dl)	1.9±0.6
ALT(IU/L)	78±13
AST(IU/L)	54±27
Hemoglobin(mg/dl)	13±2.2
Leucocyte(/mm3)	4900±500
Lactate(L/mmol)	9±3.8