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10.4103/2452-2473.329634

The effects of synthetic cannabinoids on the cardiovascular system: A case–control study

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Submitted: 07-12-2020

Revised: 01-01-2021

Revised: 21-01-2021

Revised: 26-01-2021

Accepted: 27-01-2021

Published: 30-10-2021

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Abstract:

OBJECTIVES: Limited clinical studies have investigated the effects of synthetic cannabinoids (SCs) on the cardiovascular system (CVS). The aim of this study was to evaluate the effects of SCs on the CVS.

METHODS: The patient group of this single-center, prospective, case–control study consisted of adult patients presenting to the emergency department (ED) with symptoms of SC use. Vital signs and electrocardiogram (ECG) after use of SC of patients were followed. A control group with a similar number of patients and patient demographics were formed following the patient admission process. Pulse rate, arterial blood pressure (ABP), and ECG of patient and control groups were compared using Mann–Whitney U and Chi-squared tests.

RESULTS: A total of 148 people were included in the study, 74 in the patient group and 74 in the control group. Systolic and diastolic ABPs of patient group were statistically significantly lower than those of the control group ($P < 0.001$). P-wave width and amplitude in the patient group were significantly higher compared to the control group ($P: 0.027$ and $P: 0.004$, respectively). QRS width on patient group ECGs was significantly higher than in the control group, while T-wave amplitude was significantly lower ($P: 0.045$ and $P < 0.001$, respectively). ST elevation was seen in 12 (16.2%) subjects in the patient group, while no ST elevation was seen in the control group ($P < 0.001$).

CONCLUSION: SCs can reduce systemic tension and SCs may cause changes in ECG, especially P wave, ST segment, T wave, and QRS. Further large-scale studies are needed to show whether these changes are associated with fatal arrhythmias or myocardial infarction.

Keywords:

Bonsai, cannabinoids, cannabis, electrocardiogram, K2, marijuana, spice

Introduction

Natural cannabis (Δ^9 -tetrahydrocannabinol [THC]) is a narcotic substance derived from the cannabis sativa plant. THC is the principal

psychoactive compound that affects the central nervous system.^[1] Synthetic cannabinoids (SCs) are a subgroup of cannabinoids and have recently become among the most commonly used novel psychoactive substances.^[2] They act through cannabinoid type 1 (CB1) and type 2 (CB2) receptors.^[3] CB1 receptors are located in the cortical and subcortical regions of the

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How to cite this article: Yeniocak S, Kalkan A, Yamanoğlu A, Öztürk S, Sögüt Ö, Metiner M. The effects of synthetic cannabinoids on the cardiovascular system: A case–control study. Turk J Emerg Med 2021;21:198-204.

Box-ED

What is already known on the study topic?

Synthetic cannabinoids (SCs) have become widespread in the last decade and their detrimental effects on human health are not yet clear. It is estimated that SCs have effects on respiratory system, neurological system, and cardiovascular system.

What is the conflict on the issue?

As on other systems, there are no clinical studies examining the cardiovascular effects of SCs and our knowledge is in the case report level.

How is this study structured?

Seventy-four patients who used SCs and 74 healthy volunteers were included in this single-center prospective case-control study.

What does this study tell us?

According to this study, SCs may cause P, T, and QRS wave and ST segment changes in the electrocardiogram and reduce in systemic blood pressure. Therefore, patients using SC should be monitored for possible cardiac arrhythmias and hypotension.

brain, in dorsal root ganglia in the spinal cord, and peripheral nerve regions responsible for pain sensation transmission, in bone, the heart, liver, kidney, vascular endothelium, and the reproductive system, while CB2 receptors are more present in immune system tissues.^[4]

SCs are colloquially known by a variety of names including "K2," "spice," "Bonsai," "Jamaica," "Armageddon," "black mamba," and "dream" and consist of more than one synthetic content, while novel elements are being added to their content almost on every day.^[5,6] Increasing the content of SCs also increases both the incidence of addiction and the effect of cannabinoids. SC use is therefore growing rapidly as an alternative to marijuana and other narcotics.^[7] With their growing and constantly changing content, SCs exhibit a broad side-effect spectrum. Although they generally involve neuropsychiatric side effects such as euphoria, anxiety, panic attack, and hallucination, cerebrovascular system side effects, respiratory system side effects, kidney damage, coma, and death have also been reported.^[8-12]

Case reports of myocardial infarction,^[10] prolonged corrected QT interval (QTc), and Mobitz type II atrioventricular block^[13] and ventricular fibrillation^[13,14] depending on the use of SCs were earlier reported. Our review of the literature revealed rare clinical studies,^[15] other than case reports, examining the effect of SCs on the cardiovascular system (CVS), a widespread health problem. The purpose of this study was to determine the effects of SCs on the CVS.

Methods

Study design and setting

This single-center, prospective, observational case-control study was performed following receipt of local ethical committee of Haseki Training and Research Hospital approval at June 17, 2017 (Approval no: 2017/422). Adult patients using SC and presenting to the emergency department (ED) in January–April 2017 were included in the study. This ED serves over 150,000 patients annually and is located in a 580-bed hospital in the center of a large metropolis. Written consent was obtained from all patients or their families.

Study population

All patients of both sexes over 18 years of age who had no trauma and presented with any complaint after SC use were admitted to the study. Patients with concomitant alcohol or other drug use, known cardiac disease, and antihypertensive and antiarrhythmic drug use were excluded from the study. The SC and other drug use of the patients were based on their own statement or the accompanying relative's declaration, ethyl alcohol levels were measured in all patients.

The control group was formed by inviting a similar number of healthy volunteers, with similar age and gender characteristics from the hospital staff and patient relatives, with no known cardiac disease and no history of use of SCs and any drugs.

Study protocol and measurements

Patients presenting to the ED with the use of SC were first assessed by an emergency medicine specialist. Patients whose initial examination and emergency intervention were completed have, respectively, been included in the study in order after consent was obtained. Pulse rate, arterial blood pressure (ABP), body temperature, respiratory rate, oxygen saturation values, and arrival electrocardiogram (ECG) were obtained. ABP was measured using a manual blood pressure device (ERKA Perfect Aneroid/Germany), together with pulse rate, by a 10-year-experienced health officer. ECGs were obtained at a speed 25 mm/s and amplitude of 10 mm/mV with Edan SE-1200 Express brand device by the same health officer. While the ECG was taken, the electrodes were placed at the standard attachment points and these points were marked. Recurrent ECGs were obtained by replacing the electrodes at the marked points. Vital signs and ECG were measured immediately if there was an additional complaint in the patients and routinely every hour if there were no additional complaints. The measurement that was furthest from the normal limits from the measurements taken until the patients' symptoms disappeared was included in the calculation. When patients were admitted to another department

from the ED or transferred, they were monitored in terms of clinical outcomes of mortality and morbidity. Once the patient group had been completed, a control group was established consisting of the same number of individuals as in the patient group, with similar age and sex characteristics. Vital signs and ECG were performed in same measuring position using devices of the same make and features in both the patient and control groups.

The ECGs obtained were evaluated by specialist cardiologists in our study team blinded to which group the ECG belonged. In addition to general rhythm analysis, all ECGs were assessed in terms of P-wave width and amplitude, presence of pathological Q wave, its width and depth if present, PR interval, R-wave width and amplitude, presence of ST elevation and amplitude if applicable, QRS width, T-wave height and amplitude, and level of the QT and QTc interval calculated with Bazzet's formula ($QTc = QT/\sqrt{RR}$). In addition, the presence of ST-segment elevation was described accordance with the American College of Cardiology, American Heart Association, European Society of Cardiology, and the World Heart Federation committee:^[16] at least two contiguous leads with ST-segment elevation 2.5 mm in men older than 40 years, 2 mm in men younger than 40 years, or 1.5 mm in women in leads V2–V3 and/or 1 mm in the other leads. ECG and vital sign data from the patient and control groups were then subjected to statistical comparison.

Data analysis

SPSS 15.0 (SPSS Inc., Chicago, IL, USA) for Windows software was used for statistical analysis. Descriptive statistics were expressed as number and percentage for categorical variables and mean, standard deviation, minimum, and maximum for numerical variables. Since numerical variables did not meet normal distribution conditions, comparisons between the two groups were performed using the Mann–Whitney U-test and Chi-squared tests. Fisher's exact test was used if the percentage of those <5 among the calculated theoretical frequencies was >20%. Proportions in groups were compared using Chi-square analysis. $P < 0.05$ was regarded as alpha significance.

Results

A total of 98 nontraumatic patients over 18 years of age who applied to ED with complaints related to SC use were included in the study, three of which was female. Seventy-four patients, three females (4.1%) and 71 males (95.9%), were included in the final analysis after exclusion criteria. The control group also consisted of 74 healthy volunteers, three of which was female. The work flow chart is presented in Figure 1. Mean ages were 25 (19–30) years in the patient group and 25 (20–30) in the control group. The members of the patient and control groups were similar in terms of sex ($P: 1.000$) and age ($P: 0.851$); no statistically significant difference was determined between them. Demographic characteristics and vital signs of the patient and control groups are shown in Table 1. Systolic and diastolic ABPs were significantly lower in the patient group than in the control group.

Mean time elapsing from the use of SC to presentation to the ED among the patients in this study was 2.19 ± 2.00 h. The earliest presentation occurred 30 min after SC use, and the latest 16 h after use. The most common cause of presentation was nausea and vomiting in 20 patients (27%), followed by altered consciousness in 14 and somnolence in 14 [Table 2].

Mean values for electrolytes and organ function tests in the patient group are shown in Table 3. Mean values for the parameters investigated were within normal ranges excluding glucose.

As a result of the analysis of ECG parameters, a significant difference was found between patient and the control group in P wave width, P wave amplitude, presence of ST segment elevation, T wave amplitude, and QRS width [Table 4].

Discussion

Analysis of patient group ECG findings revealed statistically significantly higher P-wave width and amplitude and QRS segment width than in the control group. T-wave amplitude was significantly lower in

Table 1: Demographic characteristics and vital signs of study subjects

	Patient group	Control group	95% CI for the difference between two medians	P
Sex, n (%)				
Male	71 (95.9)	71 (95.9)	-	1.000
Female	3 (4.1)	3 (4.1)	-	1.000
Age (years), median (IQR 25%-75%)	25 (19-30)	25 (20-30)	0.5 (-3-4)	0.851
SBP (mmHg), median (IQR 25%-75%)	110 (100-120)	120 (110-126)	-10 (-10--10)	<0.001
DBP (mmHg), median (IQR 25%-75%)	70 (60-70)	70 (70-80)	0 (-7-7)	<0.001
Pulse rate (/min), median (IQR 25%-75%)	81 (68-94)	80 (71-97)	1 (-8-10)	0.525

CI: Confidence interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, IQR: Interquartile range

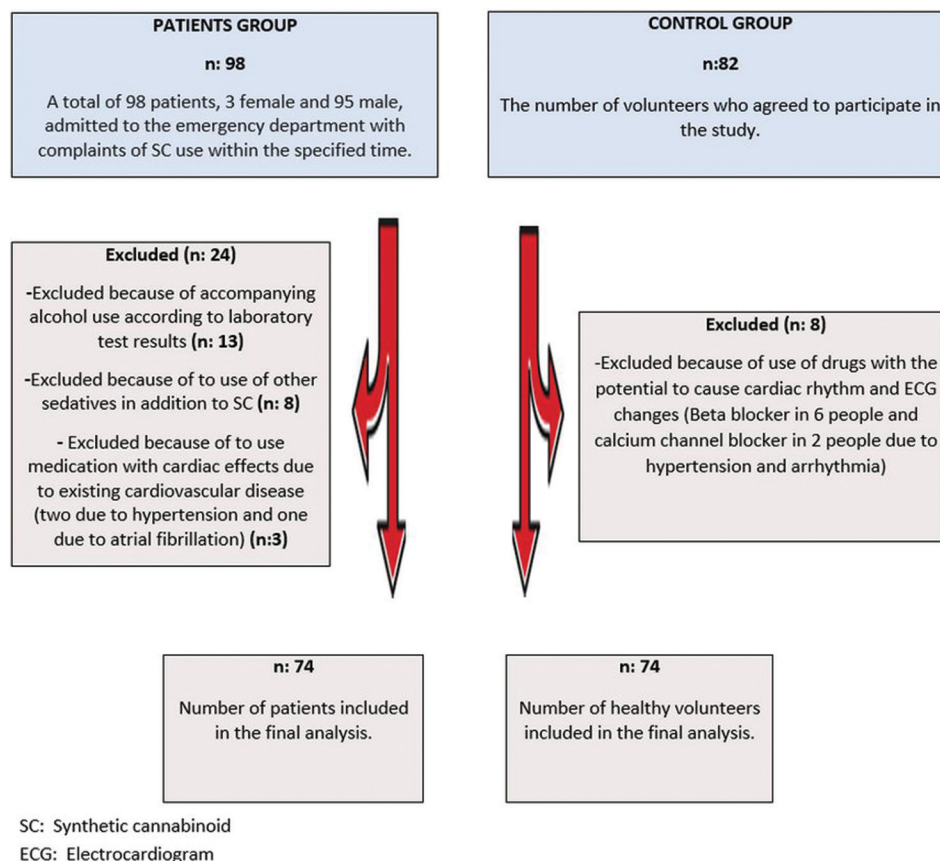


Figure 1: The workflow chart

Table 2: Presenting symptoms of patients depending on the use of synthetic cannabinoid

	n (%)
Time elapsing from SC use to presentation to the ED (min)	139±120 (30-960)
Principal cause of presentation	
Nausea-vomiting	20 (27.0)
Altered consciousness	14 (18.9)
Somnolence	14 (18.9)
Stupor	10 (13.5)
Agitation	9 (12.2)
Dizziness	4 (5.4)
Headache	2 (2.7)
Fear	1 (1.4)

ED: Emergency department. SC: Synthetic cannabinoid

Table 3: Laboratory test results of the patient group

	Median (IQR 25%-75%)	Minimum-maximum
Ca ⁺⁺ (mg/dL)	9.2 (8.9-9.5)	7.8-10.4
Na ⁺ (mEq/L)	138 (136-139)	118-146
K ⁺ (mmol/l)	3.5 (3.3-3.8)	3-5.5
Glucose (mmol/L)	113 (102-132)	85-573
Urea (mg/dL)	29 (23-34)	16-69
Creatinine (mg/dL)	0.8 (0.8-0.9)	0.6-1.3
AST (IU/L)	24 (19-32)	12-77
ALT (IU/L)	17 (13-27)	6-85

Ca⁺⁺: Calcium, Na⁺: Sodium, K⁺: Potassium, AST: Aspartat Aminotransferaz, ALT: Alanin aminotransferaz, IQR: Interquartile range

the patient group than in the control group. Previous studies on this subject are few in number. Ozturk *et al.* reported significantly higher P-wave dispersion and QT interval at ECG analysis of 35 patients using SC compared to a control group, but no significant finding was observed in terms of T-wave measurements.^[17] Aydin Sunbul *et al.* examined the ECGs of 72 SC users and determined a significant increase in P-wave dispersion in the patient group.^[15] CB1 suppresses intracellular adenylyl cyclase and cAMP levels through G-protein. Activation of G-protein-coupled receptors suppresses voltage-dependent Ca⁺² channels and activates K⁺ channels. As a result of these changes, a decrease occurs in cellular excitability and neurotransmitter release by intracellular presynaptic hyperpolarization.^[18] The increase in amplitude and width of the P-wave, a marker of atrial conduction abnormalities and atrial arrhythmia development, may be attributed to the decelerating effect of SCs on electrical conduction from the sinoatrial nodule through the CB1 receptor.

ST elevation criteria were present in 7 (9%) members of the patient group and all of them were in chest derivations. Six (8%) of the ST elevations were in V2–3 derivations and one (1.3%) was in V3–6. No findings in favor of myocardial infarction were determined at cardiac marker follow-up.

Table 4: Electrocardiographic measurements of the study subjects

	Patient group, median (IQR 25%-75%)	Control group, median (IQR 25%-75%)	95% CI for the difference between two medians	P
P wave width (ms)	120 (80-120)	100 (80-120)	20 (10-30)	0.027
P wave amplitude (mm)	1 (1-2)	1 (0.5-1.5)	0 (-0.2-0.2)	0.004
Q wave presence, n (%)	20 (27)	28 (37.8)	-	0.160
Q wave depth (mm)	0 (0.1-0.6)	0 (0-0.5)	0 (0-0)	0.353
Q wave width (ms)	0 (0-25)	0 (0-20)	0 (0-0)	0.631
PR interval (ms)	180 (160-220)	200 (160-240)	-20 (-40-0)	0.246
R amplitude (mm)	10 (6-12)	8 (6-12)	2 (0.2-4)	0.278
R wave width (ms)	60 (40-80)	50 (40-80)	10 (0-20)	0.305
ST elevation, n (%)	7 (9)	0 (0)	-	0.013
T wave amplitude (mm)	2 (2-3)	3 (2-4)	-1 (-1.7--0.3)	<0.001
T wave width (ms)	200 (160-240)	200 (160-240)	0 (-20-20)	0.626
QRS width (ms)	80 (80-120)	100 (80-120)	-20 (-10--30)	0.045
QT interval (ms)	440 (380-600)	445 (360-565)	10 (-80-70)	0.475
QTc (ms)	448 (411-476)	423 (397-470)	30 (0-50)	0.068

CI: Confidence interval, IQR: Interquartile range

Cardiac symptoms (palpitation, distress, and anxiety) were present in only one of these patients. ECG indicating Type 2 Brugada characteristics was present in one patient, who was placed under cardiological monitoring from that perspective. No ST elevation was determined in any patient in the control group. Although the number of studies on the subject is low, the fact that some cases of myocardial infarction with ST elevation have been reported supports this study.^[19,20] We think that the ST elevation may have resulted from SCs causing coronary spasm and increased oxygen consumption through receptors,^[3] and despite being characteristic of early repolarization, previously reported cases of sudden death^[21] may be related to impairment of the heart's oxygen requirements due to underlying coronary plaques. In addition, other possible causes may be sympathetic stimulation and coronary vasospasm due to accumulation of noradrenaline, vasospasm, plaque rupture, thrombus aggregation, and myocardial oxygen supply imbalance.^[22,23]

Some studies have maintained that SC use can lead to atrial fibrillation (AF).^[15] P-wave morphology differed in SC-user patients in our study compared to the control group. However, no AF occurred in patients. The change in the P-wave in patients using SCs in our study may support the idea of a disposition to AF.

T-wave amplitude was significantly lower in our patient group than in the control group. There was no significant difference between the groups in terms of T-wave widths. QRS width was significantly higher in our patient group than in the control group. It has previously been suggested that SC use can give rise to hypokalemia and that this can result in cardiac arrhythmias.^[4,21] We think that our patient group T-wave amplitudes being significantly higher than those in the control group may be due to SCs causing ventricular repolarization with low voltage independently of potassium.

Although a case of ventricular fibrillation associated with SC use has been reported, the underlying etiology could not be fully explained.^[14] The different QRS width and T-wave amplitude in our patient group compared to the control group suggest that an arrhythmia risk may associated with SC. It has been suggested in previously reported cases that SCs are capable of causing prolonged QTc and Mobitz type II block.^[15] However, we determined no significant difference between our patient and control groups in terms of QTc width or PR intervals. No atrial or ventricular arrhythmia occurred during observation in any members of our patient group.

Both systolic and diastolic ABPs in patient group were significantly lower than those in the control group. The lowest systolic ABP in patients group was 85 mmHg, and the lowest diastolic ABP was 50 mmHg, but no patients required inotropic support apart from fluid. There have been case reports and series indicating that SCs result in hypotension.^[8,24] From that perspective, our findings were compatible with the previous literature. We attribute the ABP being significantly lower in the patient group compared to the control group to the dose-dependent sedative effects of SCs masking sympathetic nervous system effects.^[25-27]

SCs cause P and P/Q-type calcium channel inhibition by lowering membrane potentials with sodium-potassium pump inhibition through reactor-mediated reaction with cell membrane voltage-gated ion channels.^[28] Neuropsychiatric symptoms associated with the sympathetic nervous system may be expected in that context. While nausea-vomiting was the most common presentation symptom in our patient population, altered consciousness was the next most common. In one previous case series involving adolescents, the most common symptom was reported as agitation and anxiety.^[8] However, agitation and anxiety were

less common causes of presentation in our study. This difference may be due to the small population in Besli *et al.*'s study and to that population consisting of children. Karabulut *et al.* retrospectively examined 61 cases of presentation to the ED due to SC use and reported altered consciousness, lethargy, and dizziness as the most common presentation symptoms. Nausea and vomiting were less common.^[29] We think that this, which is not in agreement with our study, may have developed due to the wide, dose-dependent side effect profile deriving from SCs entering the market at different times and places having constantly changing contents.

Limitations

This study was performed in a single center and with a limited number of patients. SC derivatives were not subjected to laboratory tests in any case. Patients with a history of substance use in addition to SC, suspected of using additional substances on the basis of examination findings, or with laboratory findings indicative of additional substance use were excluded from the study. Identification of SC derivatives, the content of which is constantly growing and changing, is not possible in our center, and only 3–4 varieties can be widely studied. However, the limited kits available for SCs, the content of which is increasing all the time, are rapidly losing reliability. Patient selection was therefore based on history, as widely employed in many other centers, and patients giving unwitnessed or contradictory statements were excluded in terms of the reliability of the study. In addition, substances other than SCs cannot be detected routinely in the emergency room in our clinic. Among the sedatives, only the ethyl alcohol level could be studied.

Conclusion

SCs use may result in increased P-wave amplitude and width, significant ST elevation, significantly low T-wave amplitude, and significant QRS width by affecting the cardiac conduction system and may constitute a risk in terms of cardiac arrhythmias. In addition, SCs may lead to reduce systemic tension. Patients presenting with SC use must be closely monitored in terms of cardiovascular events.

Acknowledgment

The authors verify and confirm that everyone who contributed to this manuscript is either listed as an author or acknowledged as a contributor in the acknowledgement section, and that the title page details any professional writing assistance or others paid to provide manuscript support.

Author contributions statement

Conception and design: Adnan Yamanoglu, Selman Yeniocak, Semi Ozturk, Asim Kalkan, Merve Metiner, Ozgur Sogut; acquisition of data or analysis and interpretation of data: Selman Yeniocak, Merve Metiner, Adnan Yamanoglu, Semi Ozturk; drafting the article or revising it critically for important intellectual content: Selman Yeniocak, Adnan

Yamanoglu, Semi Ozturk, Asim Kalkan, Ozgur Sogut; final approval of the version to be published: Asim Kalkan, Ozgur Sogut, Adnan Yamanoglu, Semi Ozturk; for all aspects of the work in ensuring that questions related to the accuracy and integrity appropriately investigated and resolved: Adnan Yamanoglu, Selman Yeniocak, Semi Ozturk, Asim Kalkan, Ozgur Sogut, Merve Mertiner.

Ethical approval

Ethical consent was obtained for this study from the local ethics committee of Haseki Training and Research Hospital with the number 2017/422, on date of 17.06.2017.

Financial support and sponsorship

None.

Conflicts of interest

None Declared.

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Yeniocak, et al.: Cardiotoxic effects of synthetic cannabinoids

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