Comparative study between acute toxicity of natural cannabis and synthetic cannabinoids

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Abstract	
	Introduction: Synthetic cannabinoids (SCs) are psychoactive substances that are gaining popularity for being available and indetectable by standardized drug tests. Synthetic cannabinoids products have similar effects to cannabis, yet are more potent, and have been associated with dangerous adverse effects.
	Aim of the study: evaluation of the dangerous effects of SCs in comparison to cannabis.
	Methods: This study was an observational retrospective cohort study including patients admitted to Poisoning Control Centre Ain Shams University Hospitals with acute toxicity of cannabis or synthetic cannabinoids over 5 years period from January 2015 to December 2019.
	Results: The study included 834 patients. SCs group included 113 patients mostly males (96%) between 13-40 years of age and due to recreational use by smoking (95%). Compared to the cannabis group, the SCs group showed a significant increase in mortality, occurrence of seizures, and need for mechanical ventilation.
	Conclusion and recommendations: SCs drugs show greater toxicity than cannabis. Further investigations of acute and long-lasting adverse effects are required.
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Key words	Synthetic cannabinoids, cannabis, seizures, coma, mechanical ventilation

Introduction

The Cannabis plant has an ancient history of medicinal and recreational use for its physiological and psychoactive effects. Globally Cannabis is by far the most widely cultivated, trafficked, and abused psychoactive substance under international control (Lucas, 2012; World Health Organization, 2016).

Synthetic cannabinoids (SCs) are cannabinoid receptor agonists with variable structural designs and potencies. They were originally synthesized as research tools or potential therapeutic agents (Øiestad et al, 2017). The use of diverse smokable herbal products ("Spice" products) containing synthetic cannabinoids has emerged as a new trend in substance abuse. As all new psychoactive substances (NPS), they induce psychoactive effects, readily available, cheap together with avoiding regulatory oversight (Zanda & Fattore, 2018).

In Egypt, synthetic cannabinoid products were introduced to the market under the names of "Strox" or "Voodoo" as an Egyptian version of spice. In 2014, the NPs known as "Voodoo-Spice-Marijuana" were added to Schedule No. 1 of the Egyptian Drugs Act. The hotline of addiction treatment under the Ministry of Social Solidarity (MOSS) reported a marked increase in Strox addicts (Hashim, 2020).

Although SCs drugs mimic the psychotropic effects of cannabis, their undesired effects are unpredictable, more severe, and more harmful than those associated with cannabis (Koby and Aviv, 2018). Accidental overdose, health problems, and adverse events may necessitate contact with poison information centers and treatment at hospital emergency departments. SCs can result in a wide range of symptoms, including speech impairments, visual and auditory hallucinations, and paranoia, which can lead to aggressive behavior (Spaderna et al 2013). Strox specifically causes loss of concentration, delirium, tachycardia, and vomiting, fainting, extreme fear of death, anxiety, heart attacks, and lethal convulsions (Schep et al 2015).

Aim of the Study

This study aimed to evaluate and compare acute toxicities of natural cannabis and synthetic cannabinoids over a 5-years period from January 2015 to December 2019.

Ethical consideration:

All data collected were anonymous and confidentiality issues were preserved. Approvals were obtained from both the director of Poisoning Control Centre -Ain Shams University Hospitals (PCC-ASUH) and Research Ethics Committee (REC) Faculty of Medicine, Ain Shams University (FWA 000017858).

Patients and Methods

This is an observational retrospective cohort study that included all patients admitted to PCC-ASUH

with acute toxicity of cannabis or synthetic cannabinoids over a 5-years period from January 2015 to December 2019.

The study included patients who were reported as acute toxicity of cannabis (hashish as a street name) or synthetic cannabinoids (Voodoo, or Strox as a street name). Patients with concomitant drug overdoses, preexisting hepatic, renal, respiratory, cardiac, or neurologic diseases were excluded.

For all included patients the following were recorded:

1. Sociodemographic data: age and sex.
2. Intoxication data: route of administration, and manner of poisoning as recorded from the patients or their relatives
3. Clinical data: including vital data (pulse, blood pressure, respiratory rate, and temperature), clinical presentations, duration of hospital stay, and outcome. Patients with respiratory distress and desaturation were exposed to mechanical ventilation.
4. Investigations: Routine investigations were done for all patients including arterial blood gases, liver enzymes (Serum AST and ALT) and kidney function (Serum Creatinine) tests. ECG was recorded at admission and repeated if needed.

Statistical analysis: Data for both groups were tabulated and statistically analysed using Statistical package for Social Science (SPSS) version (15) software (SPSS Inc, USA). Qualitative variables were expressed as frequencies (n) and percentages (%). Chi-square test was used to test the association between qualitative variables. P-value of 0.05 or less is considered significant, P-value of 0.01 or less is considered highly significant and P-value of > 0.05 is considered non-significant. (Norusis, 1997)

Results:

The current study included a total of 834 cases, furtherly divided into 2 groups:

- Cannabis toxicity group including 721 patients.
- SCs toxicity group including 113 patients. SCs were reported as voodoo in 42% (n=47), and as Strox in 58% (n=66).

Regarding age and gender distribution, a statistically significant difference was found between the 2 studied groups. Cannabis group patients were mostly below 13 years of age in contrast to those SCs group who were mainly between (13-40) years. A minor number of cases above the age of 40 were recorded in both groups. Most patients (96%) in SCs group were males (n=108) compared to 52% (n=374) in cannabis group (Table 1).

Intoxication data showed a statistically significant difference between the 2 studied groups. Most patients of the SCs group (95%) were due to inhalation by smoking while (96.2%) of the cannabis group were due to oral ingestion. Moreover, intoxication was mainly linked to substance abuse in the SCs group in contrast to accidental poisoning in the cannabis group (Table 1).

Mortalities occurred only among SCs group patients (7%). Cannabis group patients (91%) needed mainly shorter periods of hospital stay (< 1day). Among SCs group patients, there was a significant increase in the period of hospital stay (2-3 days in 36%,> 4days in 9%) (Table 2).

A significantly higher incidence of abnormalities in vital data was found among the SCs group including tachycardia (26.5%), hypertension (10.6%), and tachypnea (28.3%) in comparison to the cannabis group. However, no statistically significant difference was found between both groups as regards the occurrence of hypothermia. Statistical analysis revealed a significant increase in the incidence of coma among the cannabis group (90%) versus (58 %) in the SCs group. Conversely, the SCs group showed a significant increase in the occurrence of agitation (30%), seizures (17%), vomiting (34%), and the need for mechanical ventilation in comparison to cannabis group patients. Ischemic changes (ST-segment depression) were only associated with the SCs group (Table 3).

Regarding laboratory abnormalities, a significantly higher occurrence of respiratory acidosis and elevated serum creatinine was noted in the SCs group compared to the cannabis group. On the other hand, there was an insignificant difference regarding the incidence of metabolic acidosis or abnormal liver enzymes between both groups (Table 3).

Table (1): Chi-square statistical analysis for distribution of age, gender, and intoxication data in the 2 studied groups

		Cannabis 721		SCs 113		Chi-square test	P
		Number	%	Number	%	χ^2	
Age	**<13**	694	96.2	6	5	601	0
	13-40	23	3.2	99	88		
	>40	4	0.6	8	7		
Sex	**Male**	374	52	108	96	76.4	0
	Female	347	48	5	4		
Route	**Oral**	694	96.2	6	5	599	0
	Inhalation	27	3.8	107	95		
Mode of poisoning	**Accidental**	694	96.2	6	5	599	0
	Overdose	27	3.8	107	95		

P<0.05: statistically significant

Table (2): Chi-square statistical analysis for distribution of survival, and period of hospital stay in the 2 studied groups

		Cannabis 721		SCs 113		Chi-square test	P
		Number	%	Number	%	χ^2	
Outcome	**Survived**	721	100	105	93	51.5	0
	Died	0	0	8	7		
Period of stay	**1 day**	656	91	62	55	119	0
	2-3 days	62	8.6	41	36		
	> 4days	3	0.4	10	9		

P<0.05: statistically significant

Table (3): Chi-square statistical analysis for distribution of clinical data and laboratory abnormalities in the 2 studied groups

		NC 721		SCs 113		Chi-square test	P
		Number	%	Number	%	χ^2	
Vital signs abnormalities	**Tachycardia**	45	6.2	30	26.5	49.2	0
	Hypertension	2	0.3	12	10.6	63.3	0
	Hypothermia	6	0.8	3	2.6	3	0.08
	Tachypnea	11	1.5	32	28.3	143.4	0
Clinical presentation	**Coma**	647	90	65	58	81.1	0
	Agitation	7	1	34	30	177.1	0
	Seizure	18	3	19	17	47.2	0
	Vomiting	49	7	38	34	75.2	0
	Respiratory failure	3	0.4	20	18	108.8	0
	Ischemic changes	0	0	4	3.5	25.6	0
Laboratory abnormalities	**Respiratory acidosis**	61	9	27	24	24.6	6.9e-7
	Metabolic acidosis	128	18	17	15	0.49	0.47
	Elevated serum creatinine	0	0	4	3.5	26.6	4.1e-7
	Elevated liver enzymes	0	0	0		25.6	4.1e-7

4.1e-7 = 4.1 x 10-7 = 0.00000041, 6.9e-7 = 6.9 x 10-7 = 0.00000069, P<0.05: statistically significant

Discussion

While natural cannabis continues to be the most widely used illegal psychoactive substance worldwide, synthetic cannabinoid receptor agonists (SCs) continue to rise in many regions as one of NPS identified by UNODC (World Drug Report, 2019). The current study evaluated the incidence, clinical manifestations, and outcome of the acute toxicity of synthetic cannabinoids in comparison to cannabis over a five-year period. It also provided an important overview on the magnitude of the problem especially with the possible underestimation of the prevalence rate of NPSs use.

In the current study acute cannabis intoxication was mostly due to unintentional oral exposure below the age of 13years which was similarly highlighted by Mohammed et al., (2021). The increasing potential for accidental exposure in infants and young children may reflect increased availability of cannabis products in the household belonging to a family member with poor

parental supervision. (Claudet et al., 2017; Noble & Kusin, 2019 & Boadu et al., 2020).

On the other hand, SCs use was a predominant problem in adolescent and adult males in the present study. The prevalence of male cases agrees with global reports; however the extent of SCs among women may be underreported due to social stigma (Mohamed et al., 2015; World Drug Report, 2018). Gunderson et al., (2014) noted that a major motivation for consuming SC drugs is the desire to experience "cannabis-like" effects without the danger of being detected since SCs are mostly undetectable via standard screening tests. Curiosity, availability, easy access, and low costs may constitute additional motives in younger age groups (Cohen and Weinstein, 2018)

Sinus tachycardia, hypertension, and tachypnea were significantly recorded in association with SCs intake. These findings were comparable to previous reports of sinus tachycardia as being the most prevalent clinical effect after SCs use often associated with

hypertension (Forrester, 2012; Castaneto et al., 2014; Abass et al., 2017). Nelson (2021) suggested that the hypertensive and tachycardic responses to Scs are mediated through a central sympathetic pressor effect with the involvement of paraventricular nucleus of the hypothalamus and amygdala. The hypertensive effects of synthetic cannabinoids are an opposing response to what is commonly seen in cannabis. This supports the view that while both act on the same system, synthetic cannabinoids produce markedly different responses compared to cannabis (López-Dyck et al., 2017; Spiller et al., 2019)

Despite being recorded in few cases in the current study, synthetic cannabinoids associated myocardial ischemia was previously reported (McKeever et al., 2015; Orsini et al., 2015; Puha et al., 2016; Hamilton et al., 2017). Myocardial ischemia was linked to the SC-induced catecholamine surge triggering coronary arterial spastic response and increasing demand to supply ratio. Other postulated mechanisms for cardiac events during cannabis smoking may involve the interference with the integrity of peripheral vascular response, THC - associated vascular inflammation and increased platelet activation (Von Der Haar et al., 2016; Singh et al., 2018; Al Fawaz et al., 2019).

It was not surprising in the present study to record disturbed level of consciousness as a prominent finding both groups, though less reported in SCs cases (58 %) compared to cannabis group (90%). Similarly, Richards et al., (2018) found that lethargy was the most common presenting symptom in accidental cannabis ingestion in children. Takakuwa and Schears (2021) noted that children were significantly more likely to experience CNS depression compared to adults owing to the relative high dose of THC per kilogram of body weight.

Monte et al., (2019) reported a predominance of neurological manifestations after SCs exposure: agitation, delirium, and toxic psychosis and seizures. Baumann et al., (2014), Tai and Fantegrossi (2014) and Banister et al., (2015), suggested that use of Scs products carries a greater risk for convulsions than does use of cannabis which agrees with the present study. These effects are most likely due to SCs-induced CB1 receptor potent full agonism in the brain. CB1 receptors are expressed by presynaptic glutamatergic or GABAergic neurons and their activation leads to decreased glutamate or GABA release with reduced excitation or suppressed inhibition, respectively (Armstrong et al., 2019).

Reports on cannabis induced vomiting in pediatric age groups after unintentional ingestion have been similarly published by Thomas and Mazor, (2017). SCs abuse leading to hyperemesis was also described (Bick et al., 2014; Tait et al, 2016). Simonetto et al., (2012) and Robinson et al., (2013) proposed that stimulation of the cannabinoid network in the gut leads to delayed gastric emptying by inhibition of peristalsis, gastroparesis, and splanchnic vasodilatation. This predominant gastrointestinal autonomic dysfunction may override the central antiemetic effect of THC inducing hyperemesis in some individuals. As potent agonist at CB1 receptors, SCs would be expected to cause prominent vomiting in comparison to cannabis (Sorensen et al., 2017; Bukke at al.2021). Additionally, increased sympathetic responsivity, cannabinoids other than THC and possible associated contaminants are speculated to be involved in the genesis of cannabinoid-related vomiting (Galli et al., 2011; Nicolson et al., 2012; Levinthal and Bielefeldt 2014).

In the current study, acid -base abnormalities were recorded among cases in both groups. The occurrence of respiratory distress and respiratory acidosis was noted among SCs cases. Forrester (2012) Abass et al., (2017) were in accordance with these results. The effect of SCs on respiration likely involves multiple mechanisms of action. Proposed theories include 1st: increased bronchial airway resistance due to stimulation of chemoreceptors and baroreceptors, 2nd: bronchiolar epithelial damage and disruption of the alveolar surfactant layer due to release of chemical gases after SCs inhalation, 3rd a net result of ineffective gas exchange leading to hypoxia, hypercapnia, and acidosis (Alon and Saint-Fleur,2017; Mark and Margaret , 2018)

As regarded liver and kidney function tests this study revealed that only 4 cases in SCs group with abnormal renal function and that was statistically significant while no liver impairment detected in both groups. Similarly, Riederer et al., (2016) reported kidney injury in 4% but hepatic injury was also detected in 1.4%. This was clarified by pathological findings consistent with acute tubular necrosis in cases of SCs associated acute kidney injury (AKI) (Bhanushali et al., 2013; Murphy et al., 2013).

Among SCs group patients, there was a significant increase in the period of hospital stay in comparison to shorter periods of hospital stay needed for patients in the cannabis group. Similar results were obtained by Hermanns-Clausen et al., 2018 where they found longer duration of symptoms due to SCs exposure. Comparably, in-hospital mortality was high (7%) and occurred only among SCs group of patients in the present study. Although lower mortality rates were recorded among SCs users by Riederer et al. (2016), these results can be justified by the higher prevalence of morbidities in the current study. Reports linked the increased risk of fatal outcome in SCs exposures to; direct toxicity, pre-existing cardiopulmonary disease, behavioral toxicity leading to excited delirium, overconsumption of other drugs, trauma, or accidents (Labay et al., 2016; Shanks et al., 2016; Darke et al., 2020).

Conclusion

Data in the present study demonstrate that the acute toxicity profile of synthetic cannabinoids clearly contrasted the relatively mild effects of ingested natural cannabis owing to the highly potent cannabinoid receptor agonism of SCs.

SCs seem to share common characteristics including tachycardia, hypertension, agitation, vomiting which generally respond to supportive care.

However, severe cardiovascular, neurological, respiratory, metabolic, and renal effects may occur in some cases necessitating longer hospital stay with high total in-hospital mortality and morbidity.

Limitations:

This study has potential limitations. This was a retrospective medical record review in a single tertiary care center and generalization of results cannot be performed. As synthetic cannabinoids and NPS cannot be detected by routine hospital toxicological screens, clinical examination was the basic tool in the diagnostic process. Records of synthetic cannabinoids use were based on self-reports from the patients or next of kin whose information may be unreliable or inaccurate.

The following points may pose additional difficulties in interpretation of clinical data:1st the inability to exclude the presence of additional ingredients or assess the amount of the products ingested or smoked, 2nd the rapid turnover of NPS, and the emergence of newer structural classes of SC, 3rd the constantly changing composition of Spice products with variable concentration of SCs by package, even of the same brand and lot, 4th adverse effects related to associated plant matter or adulterants cannot be ruled out.

Recommendations

Further investigation of their chronic effects is required as well as better detection and controlling measures against its usage spread. There is a critical demand to increase awareness of the serious hazards of synthetic cannabinoids among the general population in countries suffering from their presence. Physicians should be trained to deal efficiently with the cases of acute intoxication of synthetic cannabis. Moreover, amendment of the law is essential to include all substances that have cannabis-like actions in the schedules of prohibited substances.

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دراسة مقارنة بين السمية الحادة للقنب الطبيعى وشبائه القنب الاصطناعية

هند الهلالى وهدى محمد صلاح الدين ١

الملخص العربي

مقدمة: تكتسب شبائه القنب الاصطناعية-و هى مواد ذات تأثير نفسي ـ شعبية لكونها متاحة ولا يمكن اكتشافها من خلال الاختبارات الموحدة للمخدرات. لشبائه القنب الاصطناعية تأثيرات مشابهة للقنب ، لكنها أكثر قوة ، وترتبط بآثار ضارة خطيرة .

الهدف من الدراسة: تقييم التأثيرات الخطيرة لشبائه القنب الاصطناعية مقارنة بالقنب.

الطريقة: كانت هذه الدراسة عبارة عن دراسة رصدية جماعية بأثر رجعي شملت المرضى المقبولين بمركز السموم بمستشفيات جامعة عين شمس و الذين يعانون من سمية حادة من القنب أوشبائه القنب الاصطناعية على مدى ٥ سنوات من يناير ٢٠١٥ إلى ديسمبر ٢٠١٩.

النتائج: اشتملت الدراسة على ٨٣٤ مريضاً .تضمنت مجموعة شبائه القنب الاصطناعية ١١٣مريضًا معظمهم من الذكور (٩٦٪) تتراوح أعمارهم بين ١٣-٤٠ عامًا وكان بسبب الاستخدام الترفيهي عن طريق التدخين (٩٥٪). أظهرت مجموعة شبائه القنب الاصطناعية زيادة كبيرة في الوفيات ، وحدوث النوبات ، والحاجة إلى التنفس الصناعى مقارنة بمجموعة القنب.

الخلاصة والتوصيات: تُظهر عقاقير شبائه القنب الاصطناعية سمية أكبر من القنب. هناك حاجة إلى مزيد من التحقيقات في الآثار الضارة الحادة وطويلة الأمد.

١.   قسم الطب الشرعي والسموم، كلية الطب، جامعة عين شمس، القاهرة، مصر