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Original Contribution

Clinical effects of reported synthetic cannabinoid exposure in patients admitted to the intensive care unit☆

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ABSTRACT

Objective: To characterize the clinical presentation and hospital course of patients with reported synthetic cannabinoid (SC) exposure requiring Intensive Care Unit (ICU) admission.
Design: Retrospective case series of patients admitted to medical or cardiac ICU.
Setting: Urban tertiary care center.
Participants: Adults ≥18 years old admitted from the emergency department (ED) in 2015.
Measurements: Demographics, Sequential Organ Failure Assessment (SOFA) scores, and clinical parameters documenting the effects and hospital course.
Results: 23 patients met inclusion criteria. Median age was 47 years (interquartile range [IQR], 32–54); 83% male; 78% black. Patients were generally tachycardic (HR > 100), (65%) and hypertensive (SBP > 140), (65%) on admission. The initial chest X-ray and ECG were abnormal in 43% and 68% of patients, respectively. Pulmonary edema and tachycardia were the most common findings. Head CT imaging was abnormal in 5% of patients. Troponin was elevated >1.0 ng/ml in 3 of 19 patients (16%). Other exposures detected on admission were marijuana (30%), alcohol (30%), and benzodiazepines (26%). The median SOFA score was 6 on admission and decreased over the next 3 days. SOFA scores were primarily driven by altered neurologic status and respiratory failure. 91% required mechanical ventilation, 30% had seizures as a part of presentation, 18% required vasopressors, and 5% needed dialysis. Median hospital and ICU lengths of stay were 2.6 (IQR 1.4–3.5) and 1.6 (IQR 0.9–2.5) days, respectively. The median hospital charge was $37,008. All patients survived the index hospitalization.
Conclusions: Patients admitted to ICU after SC exposure exhibit significant organ dysfunction, particularly neurologic and respiratory. Prognosis is good with supportive care.

1. Introduction

Synthetic cannabinoids (SCs), sometimes referred to as "K2" or "Spice," are novel psychoactive substances, which are increasingly abused in the United States [1]. These synthetic chemicals are typically sprayed on plant material, which is then smoked or ingested. In the United States, these products were unregulated and sold openly in smoke shops, online, and at gas stations until 2010, when the Drug Enforcement Agency designated the most common forms as Schedule-I substances [2]. Today, all 50 states have banned SCs and several states have laws restricting marketing, display and advertising of these products. The adverse effects of SC toxicity are heterogeneous and can include anxiety, agitation, emesis, hallucinations, convulsions, psychosis, tachycardia, and unresponsiveness [3]. Serious systemic effects include stoke, renal failure, myocardial infarction, respiratory failure, and death [2]. As of May 2015, >40 deaths in the US were associated with SC use [1].

Previous research has focused on presentation and outcomes of patients who were reported to poison control centers or seen in the ED [4,5]. Other studies documented significant differences between SCs and traditional marijuana, with agitation, neurotoxicity, and cardiotoxicity more pronounced in patients who used SCs [6]. Despite well documented severe effects of SC use, literature regarding the hospital course and outcomes after SC intoxication is scarce. Further research is necessary to improve physician understanding of the potential harmful effects of SC use and to identify those patients at greatest risk for adverse outcomes. This study characterizes the clinical effects and hospital course of adult patients with reported SC exposure admitted to the ICU.

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2. Methods

This is a retrospective case series of patients ≥18 years of age admitted to the medical or cardiac ICU from the ED of a single urban tertiary care center, between January 1 and December 31 of 2015 with reported SC exposure. Exclusion criteria encompassed those patients under the age of 18, those initially transferred from outside facilities, and intoxications without clear history of SC use on presentation or only distant SC use.

The electronic medical record was used to create a comprehensive census of all patients admitted to ICU from the ED during the study period. Identified patient records were screened for the following key words: "altered", "drug", "tox", "K2", "spice", "synthetic", "overdose", "cannabinoid", and "cannabis". Cases were then individually reviewed by the primary investigator to identify those patients with strongly suspected or reported SC exposure. This included patients with one or more of the following: admitting to SC use on presentation or during the hospital course, bystander report of SC use prior to presentation, as well as intoxicated patients possessing SC products at the time of admission as documented in the chart. Identified cases were analyzed by the primary data collector. Cases without clearly documented exposure to SC were excluded from the cohort. Due to the retrospective nature of the study, the exact route of exposure is not available.

Clinical parameters were collected by a team member blinded to the purpose of the study.

Basic demographic variables, symptoms at presentation, vital signs, ED diagnosis, Glasgow Coma Scale (GCS) scores, laboratory values, toxicology screen results, electrocardiogram results, chest x-ray, and neurologic imaging we recorded. Radiologist reports were used to document abnormalities. Hospitalization charges were determined from the discharge bill. Organ dysfunction was defined as a SOFA score above 0. Organ failure was retrospectively quantified based on SOFA scores calculated daily for the first three days, followed by every other day for the duration of the ICU stay. Additionally, the severity of illness was characterized by recording the number of ventilator days, days on vasopressors, days of renal replacement therapy, rates of endotracheal intubation, and central venous and arterial catheterizations. Intensive care unit length of stay (LOS), hospital LOS, and mortality were documented, and, when available, the known or suspected type of SC was logged, as well. Data were securely stored and analyzed using REDCap data management software. Statistical analysis was performed using the analytics tools of the REDCap software. The study was conducted in compliance with HIPPA and all applicable institutional, state, and local requirements and approved by the institutional review board.

3. Results

Twenty-three out of 1724 patients screened met inclusion criteria during the study period. Their baseline characteristics are shown in Table 1. The median age was 47 years (IQR 32–54); 83% were male; 78% were black, 9% were Hispanic. The most common presenting complaint was being "found unresponsive" (52%). Other common presenting complaints included "altered mental status" (26%), and "seizure" (17%). The most common concomitant exposure was alcohol (30%). Marijuana and benzodiazepines were detected in 30% and 26% of patients respectively (Fig. 1). Initial vital signs were generally abnormal, with most patients exhibiting hypertension (65%) and tachycardia (65%). Hypoxia (02Sat < 88%), requiring oxygen supplementation, was observed in 57% of patients on admission. None of the patients with a documented temperature were febrile (>100.4F) on admission. The median values for the initial vital signs were: temperature (C) 36.7°, heart rate (HR) 113 beats/min, systolic blood pressure (SBP) 155 mm Hg, diastolic blood pressure (DBP) 90 mm Hg, respiratory rate (RR) 16 breaths/min, pulse oximetry 98% (Table 2).

Laboratory values demonstrated a variety of abnormalities. Creatinine kinase (CK) levels were available for 20/23 patients and were elevated (>200 U/l) in 48% of patients, median peak CK level was 645 U/L (IQR 250–1486 U/l). Renal dysfunction (Cr > 1) and lactic acidosis (>2 mmol/l) was seen in 39% and 44% respectively. One patient required dialysis (Table 2). Troponin was checked in 19/23 patients with 16% of patients showing significantly elevated levels, >1 ng/ml.

Table 1
Characteristics of patients admitted to the ICU after SC exposure.

Characteristic	Cases (N = 23)
Median age (years)	47 (IQR 32–54)[a]
Gender	83% male
Race	78% Black, 9% Hispanic, 9% Caucasian and Asian
Initial total SOFA score (out of 24)	6 (IQR 4–7.5)
Neurologic dysfunction, SOFA > 0	91%
Respiratory dysfunction, SOFA > 0	65%
Renal dysfunction, SOFA > 0	39%
Cardiovascular dysfunction, SOFA > 0	22%
Coagulopathy, SOFA > 0	17%
Liver dysfunction, SOFA > 0	9%
Median GCS at ICU admission	6(IQR 3–8)
Abnormal chest X-ray	44%
Abnormal ECG	68%
Median ventilator days	0.88 (IQR 0.56–1.39)
Median ICU LOS (days)	1.6 (IQR 0.9–2.5)
Median hospital LOS (days)	2.6 (IQR 1.4–3.5)
Median hospitalization charge ($)	37,008 (IQR 25,609–51,705)

[a] IQR = Interquartile range.

All patients had an admission chest X-ray, which was abnormal in 44% of cases. The most common finding was pulmonary edema, seen in 30%. Head CT imaging was performed in 21/23 cases and was abnormal in 5% of patients. 19/23 patient had an ECG performed which was abnormal in 68% of patients. The most frequent findings were tachycardia and abnormal intervals, including QTc prolongation (>450 ms). Heart catheterization was performed in two patients with troponin elevation, as others were deemed to have demand ischemia. One patient had clean coronaries and the second patient was found to have proximal left anterior descending artery disease, which required stenting, as well as other high-grade stenosis. He returned to the hospital with chest pain in the setting of SC use and was found to have in-stent thrombosis.

The peak median SOFA score was six and was recorded on admission. Median SOFA scores then decreased over the next three days (Fig. 2). Persistently elevated values were seen in patients requiring continued ICU care after day 3. Those discharged from ICU were excluded from further SOFA score calculation. SOFA scores were primarily driven by abnormal neurologic status and respiratory failure, but dysfunction was seen in all six organ systems assessed.

91% of patients required mechanical ventilation, 18% required vasopressors, and 5% needed dialysis. 30% of patients had seizures as a part of their presentation. Other invasive procedures included central and arterial lines (9%), heart catheterization (9%), and lumbar puncture (4%). Median hospital and ICU lengths of stay were 2.6 (IQR 1.4–3.5) and 1.6 (IQR 0.9–2.5) days, respectively. The median hospital charge was $37,008 (IQR $25,609–51,705). All patients survived the index hospitalization with one patient suffering a cardiac arrest during the admission and one patient dying on a subsequent hospitalization during the study period.

4. Discussion

Calls to poison control centers related to SCs have risen a staggering 229% for the first half of 2015, compared to the same time in 2014. >11% of the callers had a major reaction that was potentially life-threatening, disabling or disfiguring [7]. Those with SC exposure are increasingly finding their way into our EDs, hospital floors, and ICUs. During the 1-year study period, 23 patients were admitted to our ICU/CCU with

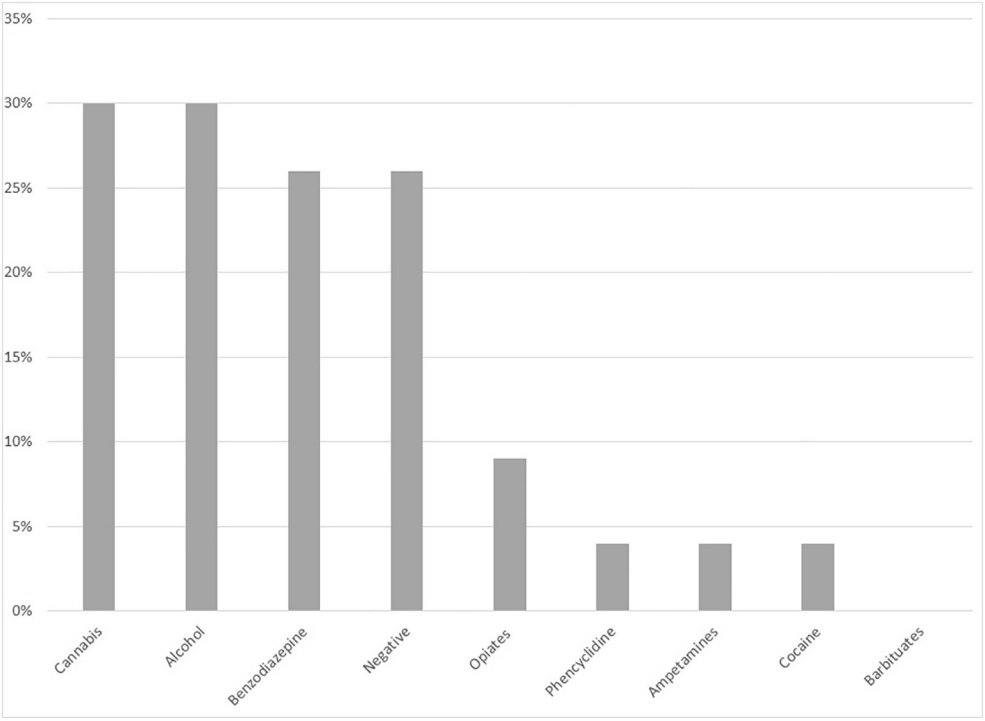

Fig. 1. Concomitant exposures.

suspected SC exposure. To our knowledge this is one of the largest such cohorts published to date.

The vast majority of subjects in this study were middle aged, African American males. This is similar to findings published in other large cohorts of patients admitted after SC exposure [8], although the average subject was older in our study. While in general the baseline demographics reflect the patient population typically seen in our urban tertiary care center, it is plausible that older age contributed to more severe adverse effects, resulting in admission to the ICU. The correlation between age and degree of organ dysfunction remains to be further elucidated.

Initial vital signs were significant for tachycardia and hypertension. Thus, it appears SCs in general exhibit a sympathomimetic effect, although bradycardia and hypotension requiring vasopressor support

Table 2
Baseline vitals, labs, and SOFA scores.

Case	Temp©	HR	SBP	DBP	RR	Pulse Ox%	Initial CK	Peak CK	Initial lactate	Peak lactate	Initial SOFA
1	36.1	90	110	55	18	97RA	65	2499	1.8	1.8	11
2	36.5	130	164	98	12	96@100% 02	794	2895	7.4	7.4	6
3	36.9	132	168	117	18	100RA[a]	699	2418	4.7	4.7	13
4	37.5	83	217	93	30	84@60%02	183	183	1.3	1.3	6
5	[b]	151	215	118	24	98@100% 02	106	251	2.5	2.5	4
6		126	159	91	18	100@100% 02	396	800	2.5	2.5	6
7[c]	**34.8**	**67**	**151**	**96**	**14**	**95RA**	**1617**	**33300**	**4.5**	**4.5**	**14**
8	37.6	147	173	98	14	100@40 % O2	1070	1070	1.5	2.6	3
9	36.3	70	95	43	16	96RA	268	268	1.5	1.5	2
10	36.7	125	124	90	12	87RA	1030	1030	1.1	1.1	8
11		137	246	125	16	100@100% 02			1.7	1.7	6
12	37	100	118	71	20	99@40% 02			4.1	4.1	1
13	36.3	45	155	54	8	99RA	426	426	0.7	0.7	6
14		92	152	104	8	100@60% 02	156	156	1.7	1.7	4
15	36.4	99	151	72	16	100@50% 02	1165	1165	1.7	1.7	4
16	37.7	113	168	106	12	100RA	247	247	0.7	0.7	4
17	37	100	114	68	40	97@45% 02			3.1	3.1	5
18	36.9	119	126	69	14	100@60% 02	132	132	0.7	1.3	4
19	36.7	123	167	99	14	95RA	303	303	0.8	0.8	2
20	36.3	101	160	80	18	89RA	1176	1176	2.1	2.1	4
21	36.8	125	129	60		78RA	489	489	2	2	7
22		125	162	71	12	93RA	207	207	2.5	2.5	12
23	36.5	63	97	60	20	100RA	4444	4444	1	0.8	13

[a] RA= Room Air
[b] Blank cells indicate missing data.
[c] Required hemodialysis.

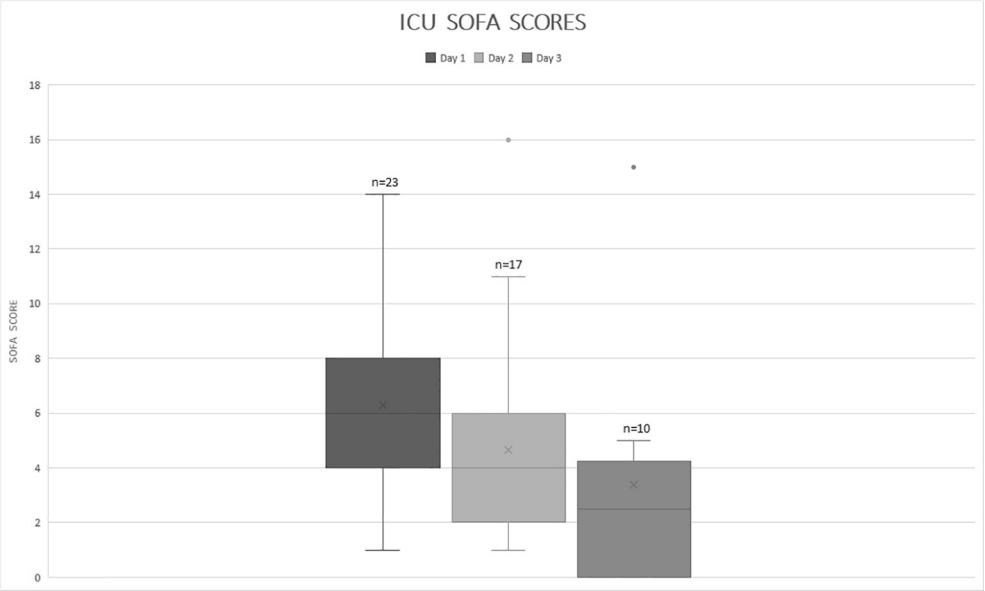

Fig. 2. SOFA scores during the ICU stay.

was also observed in a minority of patients. These divergent effects could possibly be explained by changes in formulations of SCs or by concomitant exposures.

The most frequent reason for ICU admission in this cohort was the need for mechanical ventilation. This is not surprising as more than half (52%) were found unresponsive and the median GCS on ICU admission was 6. This is similar to other cohorts of patients admitted to ICU after SC exposure where 55% were unresponsive on presentation and 82% required intubation [9]. Additionally, seizures, refractory to treatment in two cases, occurred in one third of our patients and severe agitation and psychosis were seen in others. Brain imaging should be considered in subjects presenting unresponsive, seizing, or with abnormal neurologic exams, as anoxic injury and stroke have been described [9,10].

Severe effects on the pulmonary system were frequently noted in our study and are likely multifactorial. Patients had a median initial respiratory SOFA score of 2, corresponding to a PaO2/FiO2 ration of <300. Respiratory insufficiency can be partially explained by direct effect on lung tissues as the most common route of exposure is inhalational [1]. Heart failure is a contributing factor, as decreased left ventricular ejection fraction and regional wall motion abnormalities were demonstrated on cardiac ultrasound in 3 cases. These patients also had elevated troponin values. Furthermore, multiple subjects had pulmonary edema and severe hypoxia without evidence of cardiac dysfunction. This implicates synthetic cannabinoids as a potential cause of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). It seems prudent to consider early intubation in those with low GCS on admission, severe hypoxia, and those with severe agitation or status epilepticus.

Atrial and ventricular arrhythmias, as well as cardiac arrest were seen in this cohort. This confirms previously documented, severe effects of SCs on the cardiovascular system [11]. The effects of SCs on contractility and Ca^{++} signaling have been shown through both cannabinoid receptors and through direct effect on ion channels. Abnormalities in inotropy, chronotropy, and conduction, such as QTc prolongation have been reported [12]. Elevated troponin values were noted in several cases in this cohort. In most cases these elevations can be attributed to supply-demand imbalances or vasospasm, Type 2 myocardial infarction, as demonstrated by one patient with clean coronary arteries on catheterization despite a significantly elevated troponin of 19 ng/ml. However, one patient did have proximal LAD occlusion from plaque rupture and subsequent in-stent thrombosis in the setting of SC use. Whether SCs can cause plaque rupture/Type 1 MI, and the mechanism by which this occurs, remains to be elucidated. Physicians should remain vigilant for cardiac dysfunction in the setting of SC use.

The adverse effects of SCs on the kidneys have been well documented [13] and were corroborated in our study. Renal dysfunction was seen in 39% of cases. The most serious case of renal failure requiring dialysis was associated with severe rhabdomyolysis. The mechanism by which SCs affect the kidneys remains unknown. Physicians should carefully monitor the renal function during admission, ensuring adequate volume resuscitation, especially in the setting of rhabdomyolysis.

Hepatic injury was seen in 8.7% of patients in our cohort. This is similar to other published data sets [14]. Although no subject in this case series had significant liver dysfunction, SC induced liver failure has been previously documented [15]. Thrombocytopenia was seen in 17.4% of patients raising the concern for SC induced coagulopathy. Furthermore, as SCs are metabolized by the hepatic system, physicians should be mindful of prolonged, severe effects in those with pre-existing liver dysfunction.

SOFA scores were calculated given their utility in estimating the level of organ dysfunction and predicting mortality during the ICU stay [16]. The initial median SOFA score was 6 corresponding to an estimated mortality risk of <33%. It was also noted that the SOFA scores decreased over the next three days further lowering the estimated mortality to <6%. SOFA scores were no longer calculated once patients were discharged from the ICU. This resulted in a decreasing number of subjects used for SOFA score calculation as the ICU stay progressed. A small number of patients who required prolonged ICU stay were noted to have rising SOFA scores, particularly after the 3rd day in the ICU. This predicts an increased risk of mortality in this subset. We suggest using SOFA scores as a clinical adjunct to monitor the degree of organ dysfunction, with rising SOFA scores indicating a higher risk of prolonged ICU stay, adverse events, and higher mortality.

Although the duration of hospitalization was relatively brief, the vast majority of patients were intubated and 18.2% required vasopressors support. Additional invasive procedures included central lines, arterial lines, and cardiac catheterization. Together this adds up to a high acuity of care and significant hospitalization charges. Given the rising numbers of SC related admissions nationwide, this represents a substantial financial and public health burden.

Our study does have a number of important limitations. Lack of point of care testing for SCs, prevented us from directly confirming exposure. Thus, we are relying on a high degree of suspicion as a proxy. Currently,

mass spectrometry and liquid chromatography analysis allows for rapid identification of SCs [17], however, such testing is generally restricted to reference labs. Efforts to develop reliable bedside testing using blood or urine are underway. We only included patients admitted to the medical and cardiac ICUs; therefore, we may have missed patients brought in to our trauma center with suspected or actual concomitant traumatic injury or those who died in the ED. We only collected data from a single, inner-city, tertiary care hospital in Washington, DC limiting the generalizability to other environments. The dominant SC formulation tends to vary geographically, as well as over time, further limiting the generalizability of the results of this study to other areas in the Unites States or abroad. To stay ahead of legislators and enforcement agencies, manufacturers frequently alter the chemical structure of SCs, resulting in varied clinical potency. While tetrahydrocannabinol (THC) is a partial agonist at the cannabinoid receptors (CB1 and CB2), many SCs are full agonists, with affinity that can be >100 times that of THC [18]. The inability to isolate the respective compounds prevents establishing a causal relationship between drug and toxic symptoms. Additionally, many of the subjects in the study had concomitant exposure to alcohol and recent exposure to other substances, as demonstrated by the results of urine drug screening. These findings are similar to results in other SC cohorts [19]. The impact of this is unclear, and co-ingestion cannot be established by UDS alone, but at least one study reported that patients with concurrent exposures present similarly to those exposed to SC only [20].

5. Conclusion

Synthetic cannabinoid exposure can lead to severe medical outcomes. It is a multisystem disorder with prominent and severe neurologic and pulmonary adverse effects. Intubation secondary to altered mental status was the most common cause of ICU admission. With proper supportive care, outcomes are good and mortality is low. Providers in the ED and ICU should be aware of the potential scope of complications from the use and abuse of these drugs.

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