

Strox: A 3-year study of intoxicated cases admitted to Poison Control Center Ain Shams University Hospitals

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Abstract

Introduction: Synthetic cannabinoids abuse is a global concern, creating new challenges for treatment services. Strox is a version of synthetic cannabinoids that emerged and became increasingly popular in Egypt. **Aim:** To study socio-demographic and clinical characteristics in addition to causes of deaths in patients with acute Strox toxicity who presented to Poison Control Center Ain Shams University Hospitals (PCCA). **Methods:** a cross-sectional hospital-based observational study was carried out on 92 patients with Strox toxicity during a 3 year period from 2018 to 2020. Recorded data included: age, gender, route, mode of exposure and vital data. Investigation including arterial blood gases (ABG), liver function tests (LFT) and renal function tests (RFT) and ECG were done. Outcome data including duration of hospital stay, intensive care unit (ICU) admission and mortality rate were recorded. **Results:** Cases were mainly in the age group between 13-40 years (82.6%), males (93.5%) and due to addiction (90.2 %). Coma and agitation were the main recorded presentations (63% and 34% respectively). Shock and respiratory failure were recorded in 12% and 22% respectively, while liver and renal impairment were recorded in 5% and 3% respectively. Severe intoxication was diagnosed in 78.3% with mortality rate 11%. Deaths were due to cardiac insults in 50% of the patients. **Conclusion:** The incidence of strox toxicity has recently increased in Egypt with high mortality rate. Cardiac and respiratory complication are the most common causes of death. Until now little is known about the pattern of acute poisoning by strox poisoning, so early recognition of severe cases and close observation in ICU with early resuscitation could help in lowering the mortality rate.

Key words

Strox, coma, agitation, liver, cardiac, mortality

Introduction

Besides traditionally abused substances, the use of the new psychoactive substances (NPS) is an alarming global problem that has become more marked in the last few decades (*Lamy et al., 2017*). NPS can be categorized into four groups: synthetic stimulants, synthetic hallucinogens, synthetic depressants, and synthetic cannabinoids. Despite the great efforts that have been made to diminish their skyrocketing use, the number of NPS is still increasing together with the number of users (*Shafi et al., 2020*).

Synthetic cannabinoids (SCs) are either sprayed on dried plant material so they can be smoked or sold as liquids to be vaporized and inhaled in electronic cigarettes. Their types are variable from country to another and their constituents are subjecting to continuous renewing by their creators to escape legal prohibition (*Farquhar et al., 2018*).

An emerging novel synthetic cannabinoid that named Strox is representing great medical and legal challenges in Egypt. SCs bind to the cannabinoid type-1 (CB1) and type-2 (CB2) receptors and produce their psychoactive and behavioral effects via CB1 receptor agonism (*Atwood et al., 2011*). As with tetra-hydro-cannabinol (THC), prolonged exposure to SCs results in tolerance to agonist effects, decreased CB1 receptor expression and signaling in specific brain regions (*Tai et al., 2015*).

Strox synthesis is an easy process that made it available with low prices in comparison with cannabis. Furthermore, the standard toxicology screens could not identify Strox users whereas natural cannabis would be traced (*Sobh and Sobh, 2020*). Strox-related toxicity could be attributed to THC, anticholinergic agents, and additives such as ketamine. Strox toxicity can occur without overdose because the type and amount of cannabinoid are varying considerably from batch to batch even within the same product (*Tellioglu, 2018*).

Acute Strox intoxication usually present with visual and auditory hallucinations, irritability, fear, and anxiety accompanied with intense aggression. Moreover, clinical effects mimicking anticholinergic toxidrome could occur after Strox smoking such as dilated pupil, increased heart rate, and dry flushed skin. Severe toxic effects can occur including respiratory depression, cardiac events including cardiac arrest, nephrotoxicity, seizures, and deep coma (*Lapoint et al., 2011*).

Acute Strox intoxication is frequently treated with supportive care and intravenous fluids to treat electrolyte and fluid disturbances. Cases with irritability, agitation, anxiety, and seizures are generally managed by benzodiazepines as a first-line treatment. Neuroleptics are also administered for acute

psychosis and agitation. Antiemetics have been administered for hyperemesis (Ziva, 2016).

Objective:

The study aimed to study the socio-demographic, clinical characteristics and causes of deaths in patients with acute Strox toxicity who presented to Poison Control Center Ain Shams University Hospitals (PCC-ASUHs).

Patients and Methods:

This study was a cross sectional observational study carried out over a three-year duration; prospectively during (2019-2020) and retrospectively during 2018. The study included all cases of acute Strox toxicity admitted to the Poison Control Center of Ain Shams University Hospitals (PCC-ASUHs). The diagnosis of Strox toxicity was based on history of exposure and/or the presence of characteristic clinical symptoms and signs (Bozkurt et al., 2014).

Exclusion criteria included patients with multiple drugs overdose, positive drug abuse screen, history of liver, renal, pulmonary, cardiac, neurological, endocrinal, or immunological diseases.

An informed written consent was taken from the patient or his/her legal guardian. Approval of the Head of PCC-ASUHs was obtained. Data were collected with consideration of confidentiality issues.

For the prospective study during the year 2019 and 2020, patients were subjected initially to complete medical history including: age, gender, route and mode of exposure from patients or his/her relatives, followed by measuring vital data and complete systemic examination.

Laboratory analysis were done on admission and repeated during the patient stay as needed including arterial blood gases (ABG), liver function tests (LFT) and renal function tests (RFT). Electrocardiogram (ECG) was done for all patients on admission and repeated as indicated.

Management and hospital disposition was done according to the patient's condition and according to the protocol of management in PCC-ASUHs. Patients with central nervous systems manifestations, hemodynamic instability, respiratory distress, or cardiac arrhythmia were admitted to the ICU department. Outcome data were recorded including duration of hospital stay, intensive care unit (ICU) admission, occurrence of complications as; cardiac arrhythmia and decompensating respiratory failure, renal impairment, liver impairment and mortality rate.

Based on survival, patients were classified into two groups: group I (survivors including 82 patients) and group II (non-survivors including 10 patients).

Statistical Analysis: The results were statistically analyzed using the SPSS software, version 17 (SPSS, Inc., Chicago, IL). Quantitative data are described as mean± standard deviation (SD) and qualitative data are described as number and percentage. Chi-square test (χ^2) was used to evaluate the differences between both groups. P values < 0.05 were considered statistically significant (Taylor, 1990).

Results:

Table (1): Age and Sex distribution in both studied groups.

This study included 92 patients presented to PCCA with Strox toxicity over 3 years period from beginning of the year 2018 to end of the year 2020. Table (1) showed that 9 patients (9.8%) were in the age group < 13 years, 76 patients (82.6%) were in the age group between 13-40 years and 7 patients (7.6%) above 40 years. Males constituted the majority of cases (93.5%). Eighty three patients (90.2%) were intoxicated due to addiction while 9 patients (9.8%) were accidental. Eighty patients (90.2%) were by smoking (Tables 2). Statistical analysis revealed no significant differences between survivors and non-survivors as regard age, sex, and mode/route of poisoning.

As regard vital data and clinical presentation table (3) showed that 20 patients (22%) had abnormal heart rate, 11 patients (12 %) had shock and 29 patients (32%) had respiratory distress. Fifty eight patients (63%) had coma, 31 patients (34%) had agitation, 15 patients (16%) had seizures, 30 patients (33%) had vomiting, and 20 patients (22%) required mechanical ventilation and 4.3% developed ECG abnormalities. Statistical analysis revealed significant increase in shock, respiratory distress, mechanical ventilation and arrhythmia in non-survivors.

As regard laboratory abnormalities table (4) showed 21 patients (23%) had respiratory acidosis, 15 patients (16%) had metabolic acidosis, 5 patients (5%) had abnormal liver function tests and 3 patients (3%) had abnormal renal function test. Statistical analysis revealed significant increase in metabolic acidosis and liver impairment in non-survivors.

The results revealed that the period of stay in the hospital were < 1day in 53 patients (58%), from 2-4 days in 33 patients (36%) and more than 7 days in 4 patients (4%). Moreover, no significant differences was found between both groups as regards period of stay (table 5). Also the results revealed that 72 patients (78.3%) were severe requiring ICU admission, while 20 patients (21.7%) were mild to moderate and hence admitted in the inpatient ward (table 6).

Recorded overall in-hospital mortality was 11% (10 cases). Causes of mortality included cardiogenic shock (5 cases), adult respiratory distress syndrome (ARDS) in 3 cases, and respiratory depression leading to bradypnea and respiratory failure not responding to mechanical ventilation (2 cases). As regards non-survivors due to cardiogenic shock, 4 patients presented with chest pain irritability and agitation then developed shock and cardiac arrhythmia. Recorded ECG abnormalities included right bundle branch block, ventricular tachycardia (VT), sinus tachycardia and rapid atrial fibrillation followed by VT. The 5th patient (child) presented with extrapyramidal manifestations and laryngospasm, mechanically ventilated, then developed ventricular fibrillation.

	Survivors N (%)	Non-survivors N (%)	Total N (%)	Chi-square test (χ^2)	P
Age/ year					
<13	8 (9.8%)	1 (10%)	9 (9.8%)	2.4	0.2
13-40	69 (84.2%)	7(70%)	76(82.6%)		
>40	5 (6%)	2 (20%)	7 (7.6%)		
Sex					
Male	76 (92.7%)	10(100%)	86 (93.5%)	0.7	0.3
Female	6 (7.3%)	0	6 (6.5%)		

P-value ≤ 0.05 statistically significant *N= number* %= percentage

Table (2): Manner of poisoning of both studied groups.

	Survivors N (%)	Non-survivors N (%)	Total N (%)	Chi-square test (χ^2)	P
Manner of poisoning					
Accidental	8(9.8%)	1(1 0%)	9 (9.8%)	0.001	0.9
Intended	74 (90.2%)	9(90%)	83 (90.2%)		
Route of poisoning					
Oral	8 (9.8%)	1(1 0%)	9 (9.8%)	0.001	0.9
Smoking	74 (90.2%)	9 (90%)	83 (90.2%)		

P-value ≤ 0.05 statistically significant *N= number* %= percentage

Table (3): Vital signs and Clinical presentation in both studied groups.

	Survivors N (%)	Non-survivors N (%)	Total N (%)	Chi-square test (χ^2)	P
Vital signs					
Abnormal heart rate	16, (19.5%)	4, (40%)	20(22%)	2.1	0.1
Abnormal blood pressure	7, (8.5%)	4, (40%)	11(12%)	8.3	0.003*
Abnormal respiratory rate	21, (25.6%)	8 (80%)	29(32%)	12.2	0.0004*
Clinical presentation					
Coma	54(65.9%)	4, (40%)	58, (63%)	2.5	0.1
Agitation	29 (35.4%)	2 (20%)	31(34%)	0.9	0.3
Seizure	14 (17%)	1(10%)	15(16%)	0.3	0.5
Vomiting	28 (30%)	2 (20%)	30(33%)	0.8	0.3
Respiratory failure needed mechanical ventilation	12 (34%)	8 (80%)	20(22%)	22.3	0.0002*
Arrhythmia	0	4(40%)	4 (4.3%)	34	0*

P-value ≤ 0.05 statistically significant * *N= number* %= percentage

Table (4): Laboratory abnormalities in both studied groups.

	Survivors N (%)	Non-survivors N (%)	Total N (%)	Chi-square test (χ^2)	P
Respiratory acidosis	18(22%)	3 (30%)	21 (23%)	0.3	0.5
metabolic acidosis	10 (12.2%)	5 (50%)	15 (16%)	9.3	0.002*
Liver function tests	2 (2.4%)	3(30%)	5 (5%)	13.1	0.0002*
Renal function tests	2 (2.4%)	1 (10%)	3 (3%)	1.6	0.2

P-value ≤ 0.05 statistically significant * *N= number* %= percentage

Table (5): Period of stay in both studied groups.

Period of stay	Survivors N (%)	Non-survivors N (%)	Total N (%)	Chi-square test (χ^2)	P
1 day	46 (50.1%)	7(70%)	53 (58%)	0.7	0.4
2-4 days	31(37.8%)	2 (20%)	33 (36%)	1.2	0.2
5-7days	2 (2.4%)	0	2 (2%)	0.2	0.6
>7days	3 (3.7%)	1 (10%)	4 (4%)	0.8	0.3

P-value ≤ 0.05 statistically significant *N= number* %= percentage

Table (6): Hospital disposition in both studied groups.

	Survivors N (%)	Non-survivors N (%)	Total N (%)	Chi-square test (χ^2)	P
Intensive care unit	62 (75.6%)	10 (100%)	72 (78.3%)	3.1	0.07
Inpatient	20 (24.4%)	0	20 (21.7%)		

P-value ≤ 0.05 statistically significant *N*= number %= percentage

Discussion

Synthetic cannabinoids use continues to be a significant public health concern. In the year 2018, Egyptian law incriminated usage of THC analogues which was rapidly followed by alteration of its constituents by providers using non-prohibited cannabinoids to escape legal prohibition. Attention to the dangers of SCs has been largely due to the severe, life-threatening toxic effects described in case reports and several studies (Cooper, 2016).

In the current study, the majority of the patients were males (93.5%), in the age between 13-40 years (82.6%), mainly intoxicated following smoking due to addiction (90.2%). Statistical analysis revealed no significant differences between survivors and non-survivors as regard age, sex, manner of poisoning and route of poisoning. Similar results obtained by Ozgur et al. (2018) in their study of 166 patients with SCs use where the age onset for SCs use was 17.25 ± 2.30 years, all the patients were males, and consumption of SCs was through inhalation (76.5%) or through oral route (22.9 %). Moreover, a Turkish research on 158 SCs users by Bozkurt et al. (2014) revealed that 94.9% of SCs users were men, with mean age of 26.1 ± 7 year. Similarly, Murat et al. (2018) reported 340 SCs users in a 3-month period and found that the mean age of the SCs users was 26.8 ± 7.5 years and 92.6% were men. Also, Marc et al. (2017) found that 95.5% were male and addiction was by inhalation. The higher rate of drug abuse in this age group can be attributed to life burden, psychological disturbances, stresses due to difficulty getting a job and marriage leading to involvement in drug abuse. (Jesslin et al., 2010). The prevalence of abuse among males can be related to the fact that males usually show external aggressive behaviors in dealing with problems in contrast to females who show auto-aggressive behavior. Consequently, suicide is more common in females and addiction is more common in males (Schepis et al., 2011).

In the present study, central nervous system manifestations were predominant as 63% of patients developed coma, 34% developed agitation, and 16% had seizures. Similarly, Ozgur et al. (2018) in their study of SCs user found that 74.1% of the patients developed hallucination, and 11.4% developed seizures. Also, Sarah et al. (2019) in their study of 107 patients with SCs abuse found that 28.5% of the patients had coma, 23.5% had agitation, 19% had seizures and 7% had hallucination. Murat et al. (2018) recorded psychotic symptoms in 78.8% of SCs users and impaired consciousness 42.3% was the most common reason for referral to the general hospital. Disturbed conscious level may be related to inhalation of xylene (aromatic hydrocarbon) added to Strox

preparations which burns easily and known for its central depressant effect. While anxiety, agitation and seizures may be related to Activation of cannabinoid receptors CB1 which decreased GABA release and results in reduced excitation and suppressed inhibition (Armstrong et al., 2019). In the current study, vomiting was noted in 33 % of the patients and 32% had respiratory distress and most of them (22%) were mechanically ventilated. Similarly Ozgur et al. (2018) in their study found that 62% of the SCs users had respiratory distress and 53% had vomiting.

Associated vomiting can be attributed to inhibitory effect off SCs on electrically induced contractions of small intestine causing delayed solid-phase gastric emptying. Thus, repetitive vomiting and abdominal pain are prominent gastrointestinal symptoms among SCs abusers (Robinson et al., 2013). Regarding associated respiratory distress, it can be attributed to stimulation of chemoreceptors and baroreceptors by SCs which increase bronchial airway resistance. Moreover, inhalation of xylene after SCs burn lead to bronchiolar damages and disrupt the alveolar surfactant leading to intra-alveolar hemorrhage and pulmonary edema with interference of gas exchange and resultant hypoxia and acidosis (Alon and Saint-Fleur, 2017).

The present study revealed that 12% of the cases had shock and 4.3% had cardiac arrhythmia. Statistical analysis revealed significant increase in shock, respiratory distress, mechanical ventilation, and cardiac arrhythmia in non-survivors. Similarly, Cooper (2016) reported that 11 patients out of 169 patients with SCs toxicity (6.5%) reported cardiovascular effects and cardiogenic shock. These results are in accordance with Davis et al. (2015) who described cardiac arrest in association with inhaled synthetic cannabis, and Mir et al. (2011) who reported three patients presented to the emergency department complaining of chest pain after the use of synthetic cannabinoid and acute MI was diagnosed in each case based on electrocardiogram changes and elevated troponin levels.

It is well known that SCs had potent effects on cardiac conduction system, direct effect on ion channels and myocytes which result in abnormalities in inotropy, chronotropy, and conduction with resultant decrease cardiac output and dysrhythmias (Von Der Haar et al., 2016).

The laboratory result in this study revealed that 39% of the cases had metabolic abnormalities namely respiratory acidosis (23%) and metabolic acidosis (16%). Liver and renal impairment were recorded in 5% and 3% respectively. Statistical analysis revealed

significant increase in metabolic acidosis and liver impairment in non-survivors. Similarly, *Besli et al. (2015)* on examining 16 patients with SCs toxicity reported that 40% presented with respiratory depression and respiratory acidosis, while *Riederer et al. (2016)* in their study of SCs patients found lower incidence of respiratory acidosis 5.4% and they also reported that 4% of the patients had acute kidney injury. Moreover *Kamijo et al. (2014)* in their retrospective study of 518 patients intoxicated by SCs in Japan found that liver dysfunction were detected in 25 patients (4.8%) and renal dysfunction in 11 patients (2%). *Murat et al. (2018)* found that increased liver enzyme levels (15.9%) were the most common laboratory findings among SCs users. In contrast *Abass et al. (2017)* found no statistically significant difference in liver and kidney function tests between the SCs patient group and the control group in their study of 17 patients with SCs poisoning admitted to the Poisoning Control Unit (PCU) Zagazig University Hospitals from July 2015 to April 2016.

Respiratory acidosis can be attributed to decreased sensitivity of chemoreceptors to carbon dioxide and ventilation perfusion mismatch while metabolic acidosis can be attributed to hypoxia following seizures and shock (*Wilkins et al., 2013*). Although SCs action on cannabinoid receptors CB2 has been associated with liver disease, the exact mechanism of acute liver injury is unknown (*Solimini et al., 2017*). However, dose-related cumulative oxidative hepatocellular necrosis was proposed as a possible mechanism (*Shahbaz et al. 2018*).

The current study revealed that 78.3 % of cases required ICU admission and this indicated severity of toxicity. Similarly *Besli et al. (2015)* on examining 16 patients with SCs toxicity found that 25% of the patients required ICU admission. Moreover *Rech et al. (2015)* reported that SCs are associated with higher rates of toxicity and hospital admissions than natural Cannabis, in contrast *Murat et al. (2018)* found that severe intoxication was diagnosed in only 7.6% SCs users. SCs are full agonists at the cannabinoid CB1 and CB2 receptor, so result in more potent effect than partial agonist effect of the natural cannabis, this responsible to more serious and severe course with more ICU admission in SCs toxicity (*mills et al., 2015*).

Recorded in -hospital mortality in this study was high (11%) in comparison with other studies. The Mississippi State Department of Health reported more than 1200 SCs-related emergency visits with related 17 deaths and 1.4% mortality rates. Also, the Alabama Department of Public Health reported more than 1000 emergency visits with SCs toxicity and 5 related deaths with 0.5% mortality rates (*Trecki et al. 2015*). The higher incidence of severity and mortality in our results could be due to stox had different chemical structures and have unknown contaminants that varies from country to another and may interact by different way with different unpredictable effect.

Conclusion:

The incidence of stox toxicity has recently increased in Egypt with high mortality rate. Cardiac and respiratory complications are the most common causes of death. Until now little is known about the pattern of acute poisoning by stox poisoning, so early recognition of sever cases and close observation in ICU with early resuscitation could help in lowering the mortality rate.

Recommendation:

There is a need to increase awareness of synthetic cannabinoids hazards among general population. Physician should be trained to deal efficiently with SCs acute intoxication. Further studies are needed to elucidate the effects of THC analogues and to identify their most abundant constituents with subsequent successful detection.

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ستروكس: دراسة لمدة ٣ سنوات لحالات التسمم التي تم حجزها بمركز علاج التسمم بمستشفيات جامعة عين شمس

هانى محمد توفيق^١

الملخص العربى

المقدمة: تعاطي القنب الصناعي هو مصدر قلق عالمي ، يخلق تحديات جديدة لخدمات العلاج. الاستروكس هو نسخة من شبائه القنب الصناعي ظهرت وأصبحت شائعة بشكل متزايد في مصر.

الهدف: دراسة الخصائص الاجتماعية والديموغرافية والسريرية بالإضافة إلى أسباب الوفيات في المرضى الذين يعانون من سمية الاستروكس الحادة الذين تم استقبالهم في مركز السموم الاكلينيكي بمستشفيات جامعة عين شمس.

طريقة البحث: تم إجراء دراسة مستعرضة قائمة على الملاحظة في المستشفى على ٩٢ مريضاً يعانون من سمية الاستروكس خلال فترة ٣ سنوات من ٢٠١٨ إلى ٢٠٢٠. وشملت البيانات المسجلة: العمر والجنس وطريقة التعرض والبيانات الحيوية. تشمل التحاليل المختبرية غازات الدم واختبارات وظائف الكبد و وظائف الكلى وتخطيط القلب. تم تسجيل بيانات النتائج بما في ذلك: مدة الإقامة في المستشفى ، ودخول وحدة العناية المركزة ومعدل الوفيات.

النتائج: كانت الحالات بشكل رئيسي في الفئة العمرية بين ١٣-٤٠ سنة (٨٢.٦٪) من الذكور (٩٣.٥٪) وكان ٩٠.٢٪ من الحالات بسبب الإدمان كما كانت الغيبوبة والتهيج هي الأعراض التقديمية الرئيسية المسجلة (٦٣٪ و ٣٤٪ على التوالي). سُجل هبوط القلب وال فشل التنفسي في (١٢٪ و ٢٢٪) على التوالي ، بينما سجل الاختلال الكبدى والكلى في (٥٪ و ٣٪) على التوالي. تم تشخيص التسمم الحاد الشديد في ٧٨.٣٪ مع معدل وفيات ١١٪. كانت الوفيات بسبب عَدم قلبية لدى ٥٠٪ من المرضى

الخلاصة: زاد معدل حدوث سمية الستروكس مؤخرًا في مصر مع ارتفاع معدل الوفيات. تعد المضاعفات القلبية و التنفسية أكثر أسباب الوفاة شيوعًا. حتى الآن لا يُعرف سوى القليل عن نمط التسمم الحاد بالتسمم الستروكس ، لذا فإن التعرف المبكر على الحالات الشديدة والمراقبة الدقيقة في وحدة العناية المركزة مع الإنعاش المبكر يمكن أن يساعد في خفض معدل الوفيات.