PATTERN, CLINICAL CHARACTERISTICS AND OUTCOME IN CASES OF CASTOR AND CROTON SEEDS INGESTION: SIX YEAR'S RETROSPECTIVE STUDY AT TANTA UNIVERSITY POISON CONTROL CENTRE

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ABSTRACT

Background: The consumption of herbal medicine to address health issues has gained a great attention since years till now. Castor and croton seeds are well-known by their therapeutic values; however intoxication by their ingestion could produce significant toxicities and even fatalities. **Aim of the work**: This study aimed to investigate the pattern, clinical characteristics and outcomes in cases of castor and croton seeds ingestion admitted to TUPCC. **Patient and Methods**: This retrospective study involved 27 cases of castor and croton seeds ingestion from start of 2017 to the end of 2022. All demographic, clinical and laboratory data of cases were reported. Outcomes in all cases were additionally recorded. **Results**: The majority of patients (63%) were unintentionally intoxicated children by castor seeds, unlike most of adults ingested croton seeds for therapeutic intention. Overall, gastrointestinal manifestations and dehydration were the most frequent. Oral burning sensation was significantly-linked to croton seed ingestion. Aspartate transaminase and blood urea were significantly elevated in pediatrics. Furthermore, high leukocytic count, electrolyte disturbance, metabolic acidosis, hypoglycemia, and elevated creatinine phosphokinase were reported. Castor seeds ingestion showed more ECG abnormalities. Overall, 33.3% of patients were ICU admitted, yet all patients had favorable prognosis. **Conclusions and Recommendations**: Ingestion of more seeds results in more severe toxicity. The long hospital stays and long lag to reach a health facility were significantly correlated with the severity of toxicity. The most effective approach to prevent unintentional toxic seeds ingestion is to raise public awareness about the harmful plants with everyone, especially children caregivers.

Keywords: *Castor, Croton, Toxicity, Pattern, Outcome.*

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INTRODUCTION

Despite of the rising technologies in pharmaceutical therapies for various diseases, up to half of the global population relies on alternative remedies, such as herbal and traditional medicines to address their health issues. Flowering plants (Higher Plants) contains thousands of chemicals that could be double edged causing morbidity and even mortality in humans and animals. Exposure to such chemicals may occur through ingestion, inhalation or even direct skin contact ***(Colombo et al., 2010; Serrano, 2018)***.

The castor oil plant (scientifically known as Ricinus communis L) is a native East African plant belongs to the Euphorbiaceae family and is the sole representative of the Ricinus genus and the Ricininae subtribe. It grows in tropical and warm regions throughout the world ***(Al-Tamimi, and Hegazi, 2008)***.

Ancient Egyptians used it for different pharmacological properties as a laxative, and a local remedy for abscess and baldness. They also identify the toxicity of castor bean seeds and recommended its use only in minute amounts ***(Longe, 2005)***.

A traditional use of castor beans for birth control have been reported**.** In India, castor oil has been used since 2000 BC in illumination and as a laxative, purgative, and cathartic. In china, Castor seed and urine have also been used in wound dressings ***(Polito et al., 2019).***

Castor seeds, also known as castor bean or *palma Christi* are oblong, light brown,

mottled with dark brown spots as demonstrated in **Figure (1)**. Ricin is released from the seeds only if the outer shell is broken by chewing or mastication ***(Bradberry et al., 2003)***. Fortunately, castor oil itself doesn't contain ricin and if so it is inactivated during the process of extraction by heat ***(Al-Tamimi and Hegazi, 2008)***.

The active principal in the castor seed is ricin which is one of the highly toxic chemicals that is concentrated in the seeds ***(Polito et al, 2019)***.

The castor bean plant also contains another glycoprotein lectin, the Ricin communis agglutinin. It doesn't produce directly cytotoxicity, yet it has affinity for the red blood cell, leading to agglutination and eventual haemolysis only clinically noteworthy after intravenous administration, not oral ingestion ***(Polito et al., 2019)***.

Ricin is atoxalbumin, a glycoprotein lectin that is composed of two chains, A and B that are linked together by a disulfide bond ***(Polito et al., 2019)***. The estimated lethal oral dose in humans approximates 1 milligram per kilogram of body weight. It was first identified by the German microbiologist, Peter Hermann Stillmark ***(EFSA, 2008)***.

There is a conflict regarding the exact amount of ricin in castor beans, but it is approximately ranged between 1% to 5% ***(Bradberry et al., 2003)***. Ricin that has been purified is a white, water-soluble powder, and it remains stable across a wide pH range ***(Al-Tamimi and Hegazi, 2008)***.

Ricin poses a significant toxicity risk when inhaled, injected, or ingested, and even if its dust contacts with eyes or skin. The A chain of ricin acts through disrupting protein synthesis within cells by removing one adenine part from the 28S ribosomal RNA loop found in the 60S subunit. Thus, it interferes with the elongation of the chain protein in the cell's ribosome leading to cellular death ***(Ujváry, and Krieger, 2010)***.

The B chain is a lectin that binds to galactose-containing glycoproteins and glycolipids which are expressed on the cellular membrane, thus facilitating the ricin entry into the cytoplasm ***(Sandvig, and van Deurs, 2000)***.

Other postulated mechanisms include apoptosis, direct cell membrane damage, changing the structure and function of cell membrane, and inflammatory cytokines-related damage ***(Day et al., 2002)***.

The clinical manifestations of castor seeds toxicity can be apparent within 6 hours' post-ingestion. They vary widely from nausea, vomiting and abdominal colic to hemorrhagic gastroenteritis, dehydration, electrolyte disturbances, and even hypovolemic shock. Between two and five days after exposure to ricin, it impacts the central nervous system causing somnolence and disturbed consciousness of variable degrees. Furthermore, it adversely affects the adrenal glands, kidneys, and the liver ***(Whitfield et al., 2017)***.

Other manifestations of hemolysis, leukocytosis, elevated liver enzymes, hyperbilirubinemia, blood glucose abnormalities, and elevated creatinine kinase have also been reported ***(Grimshaw et al., 2013; Bradberry, 2016)***. Miosis and mydriasis have been also described. Also, fever may start 30 minutes to two hours after ingestion of 1 to 4 castor beans ***(Al-Tamimi and Hegazi, 2008)***.

Gastrointestinal decontamination should be considered for potentially toxic ingestions including activated charcoal. The mainstay of treatment of castor seeds ingestion is supportive and symptomatic ***(Behrman et al., 2003)***. Fortunately, with meticulous supportive care, most intoxicated patients have a promising recovery outcome ***(Schep et al., 2009)***.

Croton tiglium L. *plant* belongs to the spurge family (Euphorbiaceae) is a native plant in South East Asia and Africa. *Croton* species have been largely used in folk medicines in urinary tract infections, indigestion, visceral pain, chronic constipation, herbal contraceptive, antifibroid and in infertility. Croton seeds are occasionally used directly on the skin for arthritis, neuralgia, dermatological conditions and chest infection, however it is now considered too hazardous for medicinal use ***(Magwilu et al, 2022)***.

The seeds contain crotin, a toxalbumin which is not expressed with oil. Four to five seeds

represent a lethal dose to humans ***(EFSA, 2008)***. The seeds also contain crotonside, a glycoprotein, which is less toxic. Croton seeds as shown in **Figure (2)** are oval, dark brown or black color with characteristic longitudinal striations ***(Gupta, 2018)***.

Croton seeds are toxic if ingested or applied to skin. The fatal period of toxicity ranges from 6 hours to three days. Upon ingestion, the toxin has a powerful irritating effect on gastrointestinal tract causing burning sensation of the mouth and throughout the entire GIT, salivation, vomiting, colic, bloody stools, and abortions in pregnant women. Hematuria, dysuria, anuria, proteinuria, hypotension, cyanosis, respiratory depression, slow pulse, and shock may occur. If the toxin is applied on the skin, it may cause itching, burning, and blistering. Dizziness and vertigo have also been reported ***(Hempen and Fischer, 2009)***.

The remnants of the croton plant must be removed from the mouth and to be rinsed with water soon following ingestion. The plant should be photographed or even brought with caution to health care facility for identification so that the diagnosis and appropriate treatment can be delivered. It is also advised not to induce vomiting owing to its strong irritant effect. Seeds or even vomitus may cause blockage of the glottis and suffocation secondary to laryngeal edema. General supportive and symptomatic care are satisfactory to manage symptomatic patients, and no antidotes are available ***(Poppenga, 2010)***. Activated charcoal should be administered within two hours after potential toxic ingestion. Endoscopic removal of toxic plant parts can be done in considerable ingestions of highly toxic plants ***(Kupper and Reichert, 2009)***.

Figure (1): Castor oil seed

Figure (2): Croton oil seed

THE AIM OF THE WORK

This work aimed to investigate the pattern, clinical characteristics and outcomes in cases of castor and croton seeds ingestion admitted to Tanta University Poison Control Centre (TUPCC).

PATIENTS AND METHODS

- **Study design and ethical consideration:**

This retrospective observational study was accomplished in TUPCC using the data of six year's interval (from the start of 2017 to the end of 2022). The Data of this research was recovered from the patients' clinical files of the TUPCC archive. The coding system was applied to keep the patients' data confidential. The study techniques went with the principles of the Declaration of Helsinki. The current study was approved by the research ethical committee, Faculty of Medicine, Tanta University (approval: 36264PR371/10/23), and by the head of TUPCC.

- **Inclusion criteria**

The study included all patients admitted with castor or croton toxic seeds ingestion of both sexes during the study period. The diagnosis was done based on history of either castor or croton seeds ingestion either by its name, full description or sample of seeds brought by patient or his/ her guardian). In addition, presence of characteristic toxic symptoms and signs of these seeds confirmed the diagnosis including (gastrointestinal symptoms, dehydration, circulatory collapse, and abnormal laboratory assays).

- **Exclusion criteria**

Patients with history of concurrent drug or other poison ingestion and any missing data were omitted out of the study.

- **Methods of the study:**

For the all studied patients, sociodemographic data including; the age, sex, and residence were obtained. Data regarding toxicity were reported; as delay time till admission, history of concomitant morbidities, mode of poisoning (intentional, accidental, homicidal) together with the shape and number of ingested seeds. Clinical characteristics of toxicity involving any symptoms appeared on the patient prior to or during admission. This included any gastrointestinal (GIT) manifestations as (local burning in the throat, nausea, vomiting,

diarrhea, number of their attacks, and abdominal colic).

The recorded data about the findings of clinical examination as; signs of dehydration, shock, hyperventilation, dyspnea and tachypnea as signs of metabolic acidosis were recorded. In addition, vital data records including; pulse rate, respiratory rate, temperature and blood pressure were also reported. Moreover, the consciousness level was reported as assessed by Glasgow Coma Scale (GCS) together with pupillary abnormalities including miosis or mydriasis.

Furthermore, the data of laboratory investigations was involved. It included arterial blood gases, serum electrolytes as serum sodium and potassium, random blood glucose level, creatinine, urea, liver enzymes and Electrocardiographic (ECG) recording. The severity of intoxication was determined using poison severity score (PSS) and from 0 to 3 according to ***Persson et al., (1998)***.

The primary patient's outcomes were recorded as improved, complicated and death. The secondary outcomes were similarly recorded including; intensive care unit admission, and length of hospital stay in hours.

Statistical Analysis:

Data analysis was performed using the Statistical Package for Social Sciences (IBM SPSS Statistics) version, version 26 for Windows (IBM Corp., Armonk, N.Y., USA). Descriptive statistics for categorical were in the form of counts and percentages. Associations between categorical variables were assessed using Fisher's exact and Fisher-Freeman-Halton exact tests. In the case of the association between the ordinal (e.g., PSS) and nominal variables, the Cochran-Armitage test was done. As for numerical variables, those following the normal distribution were summarized as the mean and standard deviation while those deviating from the normal distribution were presented as the median and interquartile range (IQR; expressed as the 25^{th} – 75^{th} percentiles). Numerical variables were compared between the groups using either the independent samples T-test for normally distributed variables, or the Mann-Whitney test for abnormally distributed variables). Spearman's rank-order correlation was done to assess the direction, strength, and significance of correlation between variables. A p-value <0.05 was selected to interpret the significance of the test results.

RESULTS

The contemporary analysis involved twenty-seven patients with acute toxic seeds ingestion. Seventeen patients (63%) aged below 18 years, while 10 (37%) were adults. No significance could be traced among the studied groups as regards their gender, residence, co-morbidities and number of ingested seeds. Notably, the median time lag till presentation was relatively long in all patients (13h) without any significant difference between either groups (p>0.05). Children significantly ingested the seeds accidentally (94.1%), however (70%) of adults ingested the seeds for therapeutic purposes (p<0.05). As regards the type of ingested seeds, children significantly ingested more castor seeds (82.4%) than adults, however adults consumed more croton seeds (60%) (p<0.05) as shown in **table (1)**.

Table (2) demonstrates insignificant difference between pediatric and adult patients concerning their clinical characteristics (p>0.05). Abdominal colic, diarrhea, and vomiting were the most common symptoms (92.6%, each) with a median of six episodes for the latter two. Dehydration, and circulatory collapse were observed in (44.4% and 33.3%) of cases respectively. Overall, oral burning sensation was noticed in (55.6%) of cases which was more frequent complaint among adults (80%) than children, yet statistically insignificant. Disorientation was noticed in nearly half of patients (48.1%) who had GCS less than 15. Pupil examination revealed mostly rounded regular reactive pupils, however 33.3% of cases had dilated pupils and only 11.1% had constricted pupils. Tachycardia was noticed in (66.7%), two children developed sins bradycardia representing (7.4%) of all studied patients and the remaining cases had normal heart rate (25.9%). In the majority of patients, respiratory rate, temperature as well as oxygen saturation were within normal ranges. Concerning the severity of cases using PSS, moderate and severe cases constituted (18.5%

and 37% respectively), on the other hand near half of cases were mild.

Table (3) demonstrates the comparison of castor and croton seeds toxicity as regards clinical, characteristics. Oral burning sensation was significantly apparent complaint among those who ingested croton seeds ($p<0.05$). No significant differences could be found between castor and croton seeds intoxicated patients as regards the occurrence of abdominal colic, number of vomiting and emesis episodes, dehydration, hypovolemic shock, tachycardia, disorientation and pupillary changes ($p>0.05$). However, these the fore-mentioned clinical characteristics were more frequently observed among castor seeds patients compared to croton seeds consumers.

Table (4) shows the ECG findings, laboratory characteristics and outcome of the studied groups. The ECG records of 80% of adult cases were normal. On the other hand, only 35.5% of children had normal ECG ($p<0.05$). Sinus tachycardia was an exclusive finding in pediatrics (52.9%). Interestingly, two children who ingested castor seeds developed sinus bradycardia representing (11.8%) of the total studied children as shown in **figure (3)**. Atrial fibrillation was traced in two adults who consumed castor seeds representing (20%) of the total adult cases as shown in **figure (4)**.

Table (1): Comparison of the sociodemographic and toxicological characters between pediatrics and adult patients (n=27).

Parameter		Total (n=27) (100%)	Pediatrics (n = 17) (63%)	Adult (n = 10) (37%)	Test statistic	p-value
Gender	Male	14 (51.9%)	9 (52.9%)	5 (50%)	FE	1.000
	Female	13 (48.1%)	8 (47.1%)	5 (50%)		
Residence	Rural	17 (63%)	12 (70.6%)	5 (50%)	FE	0.415
	Urban	10 (37%)	5 (29.4%)	5 (50%)		
Co-morbidities	No	20 (74.1%)	14 (82.4%)	6 (60%)	FE	0.365
	Asthmatic	5 (18.5%)	3 (17.6%)	2 (20%)	FE	1.000
	Hypothyroidism	1 (3.7%)	0 (0%)	1 (10%)	FE	0.370
	Peptic ulcer	1 (3.7%)	0 (0%)	1 (10%)	FE	0.370
Seed name	Castor seed	18 (66.7%)	14 (82.4%)	4 (40%)	FE	0.039*
	Croton seed	9 (33.3%)	3 (17.6%)	6 (60%)		
Amount	Median [IQR]	4 [3 - 5]	4 [3- 5]	4 [3- 5]	Z = 0.128	0.902
	Min - Max	1 - 6	1- 5	1.00 - 6.00		
Manner	Accidental	16 (59.3%)	16 (94.1%) $+	0 (0%) $-	X^2_{FFH} = 25.551	<0.001*
	Suicidal	4 (14.8%)	1 (5.9%)	3 (30%)		
	Therapeutic	7 (25.9%)	0 (0%) $-	7 (70%) $+		
Delay time	Median [IQR]	13.00 [7.00 - 17.00]	16.00 [10.00 - 21.00]	11.00 [7.00 - 14.00]	Z = 1.006	0.334
	Min - Max	1.00 - 48.00	1.00 - 48.00	2.00 - 36.00		

*FE: Fisher's exact test; IQR: interquartile range (25^{th} – 75^{th} percentiles); Max: maximum; Min: minimum; X^2_{FFH}: Fisher-Freeman-Halton exact test; Positive $ indicates that the percentage here is significantly higher than expected; Negative $ indicates that the percentage here is significantly lower than expected; n=number; * significant at p<0.05.*

Table (2): Comparison of the clinical characteristics and Poison Severity Score between pediatrics and adult patients (n=27).

Parameter		Total (n=27) (100%)	Pediatrics (n = 17) (63%)	Adult (n = 10) (37%)	Test statistic	p-value
Oral Burning sensation	Yes	15 (55.6%)	7 (41.2%)	8 (80%)	FE	0.107
	No	12 (44.4%)	10 (58.8%)	2 (20%)		
Abdominal colic	Yes	25 (92.6%)	17 (100%)	8 (80%)	FE	0.128
	No	2 (7.4%)	0 (0%)	2 (20%)		
Diarrhea	Yes	25 (92.6%)	17 (100%)	8 (80%)	FE	0.128
	No	2 (7.4%)	0 (0%)	2 (20%)		
Diarrheal episodes	Median [IQR]	6 [4 - 10]	8 [2 - 10]	6 [5 - 7]	Z = 0.412	0.711
	Min - Max	1 - 15	1 - 15	4 - 15		
Vomiting	Yes	25 (92.6%)	17 (100%)	8 (80%)	FE	0.128
	No	2 (7.4%)	0 (0%)	2 (20%)		
Vomiting episodes	Median [IQR]	6 [3 - 9]	8 [3 - 9]	5 [2 - 15]	Z = 0.148	0.887
	Min - Max	1 - 20	3 - 10	1 - 20		
Dehydration	Yes	12 (44.4%)	9 (52.9%)	3 (30%)	FE	0.424
	No	15 (55.6%)	8 (47.1%)	7 (70%)		
Hypovolemic shock	Yes	9 (33.3%)	5 (29.4%)	4 (40%)	FE	0.683
	No	18 (66.7%)	12 (70.6%)	6 (60%)		
GCS	15	14 (51.9%)	9 (52.9%)	5 (50%)	FE	1.000
	<15	13 (48.1%)	8 (47.1%)	5 (50%)		
Pulse	Normal	7 (25.9%)	5 (29.4%)	2 (20%)	X^2_{FFH} = 1.437	0.556
	Tachycardia	18 (66.7%)	10 (58.8%)	8 (80%)		
	Bradycardia	2 (7.4%)	2 (11.8%)	0 (0%)		
Hypo /hypotension	Normal	18 (66.7%)	11 (64.7%)	7 (70%)	FE	1.000
	Hypotension	9 (33.3%)	6 (35.3%)	3 (30%)		
Tachypnea /normal	Normal	23 (85.2%)	13 (76.5%)	10 (100%)	FE	0.264
	Tachypnea	4 (14.8%)	4 (23.5%)	0 (0%)		
Pupil	Normal	15 (55.6%)	8 (47.1%)	7 (70%)	X^2_{FFH} = 2.023	0.469
	Constricted	3 (11.1%)	3 (17.6%)	0 (0%)		
	Dilated	9 (33.3%)	6 (35.3%)	3 (30%)		
Temperature categories	Normal	23 (85.2%)	13 (76.5%)	10 (100.0%)	FE	0.264
	Fever	4 (14.8%)	4 (23.5%)	0 (0.0%)		
Oxygen Saturation (So2)	Mean ± SD	96.44 ± 2.14	96.82 ± 1.74	95.80 ± 2.66	T = 1.213	0.236
	Min - Max	92.00 - 100.00	95.00 - 100.00	92.00 - 100.00		
Poison Severity Score (PSS)	1 (mild)	12 (44.4%)	6 (35.3%)	6 (60%)	X2L = 0.300	0.667
	2 (moderate)	5 (18.5%)	5 (29.4%)	0 (0.%)		
	3 (severe)	10 (37%)	6 (35.3%)	4 (40%)		

*FE: Fisher's exact test; IQR: interquartile range (25^{th} – 75^{th} percentiles); Max: maximum; Min: minimum; t: independent samples t-test; X^2_{FFH}: Fisher-Freeman-Halton exact test; Z: Mann-Whitney test; * significant at p<0.05.*

Table (3): Comparison of castor and croton seeds toxicity as regards clinical, characteristics (n=27).

Parameter		Total (n=27) (100%)	Castor seeds (n = 18) (66.7%)	Croton seeds (n = 9) (33.3%)	Test statistic	p-value
Oral Burning sensation	Yes	15 (55.6%)	6 (33.3%)	9 (100.0%)	FE	0.001*
	No	12 (44.4%)	12 (66.7%)	0 (0.0%)		
Abdominal colic	Yes	25 (92.6%)	18 (100.0%)	7 (77.8%)	FE	0.103
	No	2 (7.4%)	0 (0.0%)	2 (22.2%)		
Diarrheal episodes	Median [IQR]	6 [4 - 10]	7 [5 - 10]	5 [4 - 15]	Z = 0.061	0.976
	Min - Max	1 - 15	1 - 15	1 - 15		
Vomiting episodes	Median [IQR]	6 [3 - 9]	8 [3 - 9]	5 [3 - 10]	Z = 0.185	0.883
	Min - Max	1 - 20	1 - 20	3 - 10		
Dehydration	Yes	12 (44.4%)	9 (50.0%)	3 (33.3%)	FE	0.683
	No	15 (55.6%)	9 (50.0%)	6 (66.7%)		
Hypovolemic Shock	Yes	9 (33.3%)	5 (27.8%)	4 (44.4%)	FE	0.423
	No	18 (66.7%)	13 (72.2%)	5 (55.6%)		
GCS	15	14 (51.9%)	10 (55.6%)	4 (44.4%)	FE	0.695
	<15	13 (48.1%)	8 (44.4%)	5 (55.6%)		
Pulse	Normal	7 (25.9%)	4 (22.2%)	3 (33.3%)	X^2_{FFH} = 1.051	0.691
	Tachycardia	18 (66.7%)	12 (66.7%)	6 (66.7%)		
	Bradycardia	2 (7.4%)	2 (11.1%)	0 (0.0%)		
Pupil	Normal	15 (55.6%)	8 (44.4%)	7 (77.8%)	X^2_{FFH} = 2.639	0.300
	Constricted	3 (11.1%)	3 (16.7%)	0 (0.0%)		
	Dilated	9 (33.3%)	7 (38.9%)	2 (22.2%)		

*FE: Fisher's exact test; IQR: interquartile range (25^{th} – 75^{th} percentiles); Max: maximum; Min: minimum; X^2_{FFH}: Fisher-Freeman-Halton exact test; Z: Mann-Whitney test; * significant at p<0.05.*

Table (4): Comparison of ECG findings, laboratory characteristics and outcome between pediatrics and adult patients (n=27).

Parameter		Total (n=27) (100%)	Pediatrics (n = 17) (63%)	Adult (n = 10) (37%)	Test statistic	p-value
Electrocardiogram (ECG)	Normal Sins Rhythm	14 (51.9%)	6 (35.3%)	8 (80%)	FE	0.046*
	Sins tachycardia	9 (33.3%)	9 (52.9%)	0 (0%)	FE	0.009*
	Sins bradycardia	2 (7.4%)	2 (11.8%)	0 (0%)	FE	0.516
	Atrial fibrillation	2 (7.4%)	0 (0%)	2 (20%)	FE	0.128
Leucocytic count (Cells/Cmm)	Leukocytosis	13 (48.1%)	10 (58.8%)	3 (30%)	FE	0.236
	Normal	14 (51.9%)	7 (41.2%)	7 (70%)		
Arterial Blood Gases Analysis	Normal	14 (51.9%)	8 (47.1%)	6 (60%)	FE	0.695
	Metabolic acidosis	13 (48.1%)	9 (52.9%)	4 (40%)		
Na Level (mEq/L)	Normal	15 (55.6%)	8 (47.1%)	7 (70%)	FE	0.424
	Hyponatremia	12 (44.4%)	9 (52.9%)	3 (30%)		
K level (mEq/L)	Normal	16 (59.3%)	9 (52.9%)	7 (70%)	FE	0.448
	Hypokalemia	11 (40.7%)	8 (47.1%)	3 (30%)		
Random blood glucose (mg/dl)	Mean ± SD	98.81 ± 17.79	94.71 ± 18.71	105.80 ± 14.36	T = 1.612	0.120
	Min - Max	72 - 139	72 - 122	89 - 139		
Normal/ hypoglycemia	Normal	18 (66.7%)	10 (58.8%)	8 (80%)	FE	0.406
	Hypoglycemia	9 (33.3%)	7 (41.2%)	2 (20%)		
Alanine aminotransferase (ALT) (IU/L)	Median [IQR]	27.00 [19 - 118]	68.00 [19 - 118]	24 [17 - 118]	Z = 0.935	0.359
	Min - Max	16- 320	16 - 320	16.00 - 230		
Aspartate transaminase (AST) (IU/L)	Median [IQR]	30 [21 - 88]	36 [28 - 88]	21 [18- 30]	Z = 2.620	0.008*
	Min - Max	17 - 230	18 - 230	17 - 116		
Creatinine (mg/dl)	Median [IQR]	0.6 [0.5 - 1.1]	0.6 [0.5 - 1.1]	0.55 [0.5 - 0.7]	Z = 0.385	0.711
	Min - Max	0.3 - 1.9	0.3 - 1.9	0.4- 1.3		
Urea (mg/dl)	Median [IQR]	30 [20- 56]	40 [30 - 56]	22 [20 - 28]	Z = 2.316	0.020*
	Min - Max	17 - 96	17 - 96	18 - 86		
Intensive Care Unit admission	Yes	9 (33.3%)	6 (35.3%)	3 (30%)	FE	1.000
	No	18 (66.7%)	11 (64.7%)	7 (70%)		
Hospital stay (hours)	Median [IQR]	55 [48 - 96]	72 [48 - 96]	48 [24- 120]	Z = 1.578	0.127
Discharge type	Min - Max	24 - 140	36 - 140	24 - 120		
	Improved	27 (100%)	17 (100%)	10 (100%)	NA	NA

*FE: Fisher's exact test; IQR: interquartile range (25^{th} – 75^{th} percentiles); Max: maximum; Min: minimum; t: independent samples t-test; X^2_L: Cochrane Armitage test for trend; Z: Mann-Whitney test; NA; non applicable; * significant at p<0.05.*

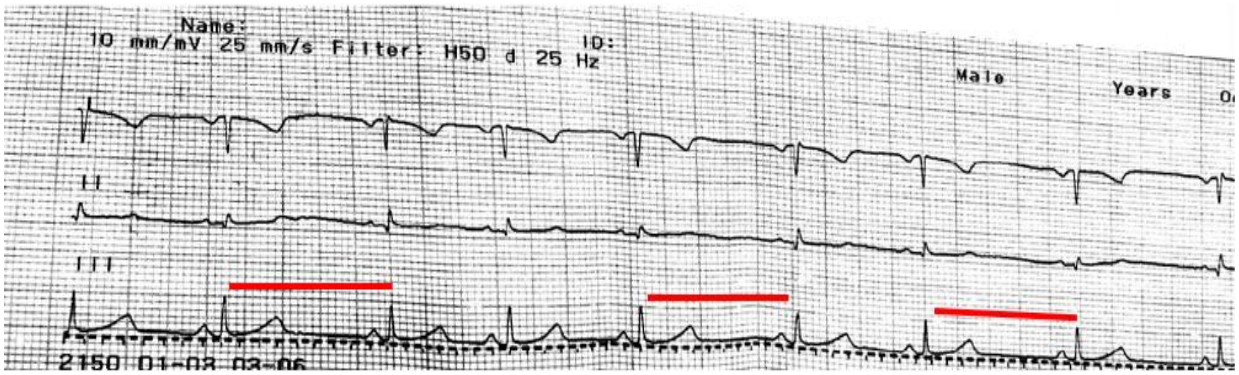

Figure (3): A male child aged 5 years alleged ingestion of 2 seeds of castor oil presented with repeated attacks of diarrhea and vomiting after 6 hours' delay. His ECG shows sinus bradycardia.

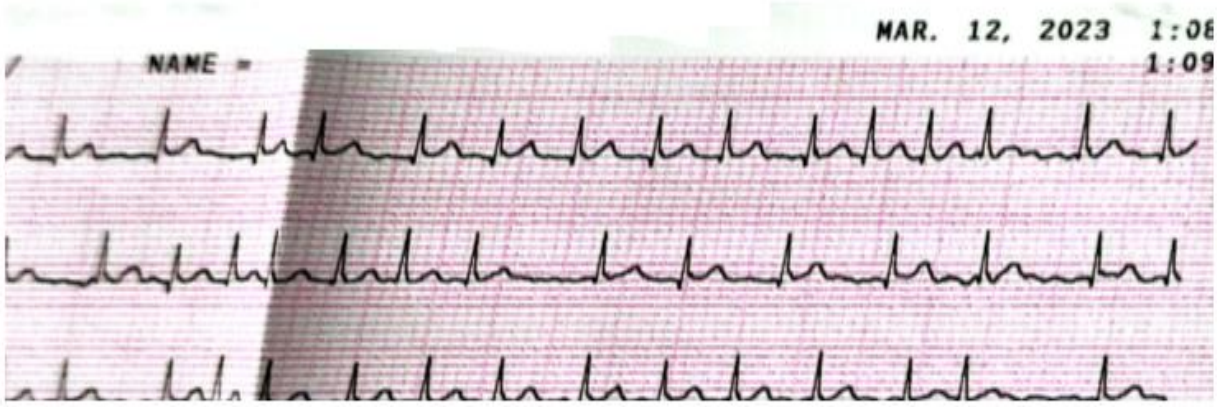

Figure (4): A female patient aged 45 years alleged ingestion of 5 seeds of castor oil presented with shock and dehydration after 14hours' delay. Her ECG shows Atrial Fibrillation.

The median values of aspartate transaminase and blood urea were significantly elevated in pediatrics compared to adults ($p<0.05$). On the other hand, no significant differences were traced as regards the remaining studied laboratory parameters. Remarkably, hyponatremia, hypokalemia, hypoglycemia, metabolic acidosis, and leukocytosis were observed in (44.4%, 40.7%, 33.3%, 48.1% and 48.1% respectively) of the total intoxicated cases.

The overall rate of Intensive Care Unit (ICU) admission was (33.3%) without significant difference among adults and pediatrics. Intoxicated children had longer median hospital stay (72 hours) compared to adults (48 hours), with the longer stay was 140 hours, yet statistically insignificant. Luckily, the whole admitted cases were discharged after complete recovery.

Discrepancies of castor oil and croton seeds toxicity as regards laboratory, ECG characteristics, and outcome is shown in **table (5)**. There were insignificant differences between castor and croton seeds intoxicated patients in regard to their AST, ALT, urea, creatinine, CPK, leukocytosis, hypoglycemia, hyponatremia, and hypokalemia ($p>0.05$). No significant differences could be observed in the incidence of ICU admission and duration of hospital stay among the studied groups.

Table (5): Comparison of castor and croton seeds toxicity as regards laboratory, ECG characteristics, and outcome (n=27).

Parameter		Total (n=27) (100%)	Castor seeds (n = 18) (66.7%)	Croton seeds (n = 9) (33.3%)	Test statistic	p-value
Alanine aminotransferase (ALT) (IU/L)	Median [IQR]	27 [19 - 118]	51.5 [19 - 118]	22 [19 - 118]	Z = 0.544	0.596
	Min - Max	16- 320	16- 286	16 - 320		
Aspartate transaminase (AST) (IU/L)	Median [IQR]	30 [21 - 88]	31.5 [28 - 78]	21 [18 - 88]	Z = 1.032	0.322
	Min - Max	17- 230	18 - 113	17 - 230		
Leucocytic count (Cells/Cmm)	Leukocytosis	13 (48.1%)	11 (61.1%)	2 (22.2%)	FE	0.103
	Normal	14 (51.9%)	7 (38.9%)	7 (77.8%)		
Arterial Blood Gases Analysis	Normal	14 (51.9%)	8 (44.4%)	6 (66.7%)	FE	0.420
	Metabolic acidosis	13 (48.1%)	10 (55.6%)	3 (33.3%)		
Na level (mEq/L)	Normal	15 (55.6%)	11 (61.1%)	4 (44.4%)	FE	0.448
	Hyponatremia	12 (44.4%)	7 (38.9%)	5 (55.6%)		
K level (mEq/L)	Normal	16 (59.3%)	10 (55.6%)	6 (66.7%)	FE	0.692
	Hypokalemia	11 (40.7%)	8 (44.4%)	3 (33.3%)		
Normal/ hypoglycemia	Normal	18 (66.7%)	11 (61.1%)	7 (77.8%)	FE	0.667
	Hypoglycemia	9 (33.3%)	7 (38.9%)	2 (22.2%)		
Urea (mg/dl)	Median [IQR]	30 [20 - 56]	30 [23 - 49]	24 [20 - 56]	Z = 0.284	0.781
	Min - Max	17 - 96	17 - 96	18 - 86		
Creatinine (mg/dl)	Median [IQR]	0.6 [0.5 - 1.1]	0.55 [0.5 - 0.9]	0.6 [0.5 - 1.1]	Z = 0.447	0.668
	Min - Max	0.3 - 1.9	0.3 - 1.9	0.4 - 1.4		
Creatinine phosphokinase (CPK) (mcg/L)	Median [IQR]	33 [28 - 55]	43 [29- 260]	28 [26 - 33]	Z = 1.728	0.085
	Min - Max	19- 360	19- 360	19 - 360		
Electrocardiogram (ECG)	Normal Sins Rhythm	14 (51.9%)	7 (38.9%)	7 (77.8%)	FE	0.103
	Sins tachycardia	9 (33.3%)	7 (38.9%)	2 (22.2%)	FE	0.667
	Sins bradycardia	2 (7.4%)	2 (11.1%)	0 (0.0%)	FE	0.538
	Atrial fibrillation	2 (7.4%)	2 (11.1%)	0 (0.0%)	FE	0.538
Intensive Care Unit admission	Yes	9 (33.3%)	6 (33.3%)	3 (33.3%)	FE	1.000
	No	18 (66.7%)	12 (66.7%)	6 (66.7%)		
Hospital stay (hours)	Median [IQR]	55 [48 - 96]	63.5 [48 - 96]	48. [48 - 96]	Z = 0.652	0.527
	Min - Max	24 - 140	24 - 140	24- 140		

*FE: Fisher's exact test; IQR: interquartile range (25^{th} – 75^{th} percentiles); Max: maximum; Min: minimum; X^2_{FFH}: Fisher-Freeman-Halton exact test; Z: Mann-Whitney test; * significant at p<0.05.*

Table (6) illustrates the severity characteristics of the analyzed cases. No significance could be verified among the mild, moderate and severe cases concerning their age, gender, residence, the manner of exposure, the type of ingested seed as well as co-morbidities except history of asthma was more commonly reported in severe cases.

On the other hand, severe cases ingested significantly more median number of seeds (5) than moderate cases (3) (p<0.05). Severe cases reached a hospital facility after a significantly longer median delay time than mild cases (16 and 7 hours respectively) and had to stay in the hospital for a significantly longer median period than mild ones (120 and 42 hours respectively) (p<0.05) on post hoc testing.

The spearman's rank-order correlation of some parameters with the severity of castor and croton seeds ingestion was done as illustrated in **table (7)**. There was a strong positive significant correlation between the severity of toxicity and hospital stay in hours (p<0.001*). Furthermore, a moderate positive significant correlation existed between the severity of cases and the delay time to reach emergency room in hours (p <0.004*). The number of ingested seeds was moderately positive although insignificantly correlated with the severity of intoxication. However, the severity of cases was negatively,

insignificantly and weakly correlated with the age of the patient (p >0.05).

Table (6): Comparison of the Severity characteristics of the studied groups (n=27).

Parameters		Poison Severity Score (PSS)			Statistical tests	
		1 (mild) (n = 12) (44.4%)	2 (moderate) (n = 5) (18.5%)	3 (severe) (n = 10) (37%)	Test statistic	p-value
Age (years)	Median [IQR]	14 [6- 49]	7 [6- 7]	10.5 [5- 39]	Z = 2.668	0.263
	Min - Max	2- 63	5- 7	2- 45		
Gender	Male	6 (50%)	2 (40%)	6 (60%)	X^2_L = 0.190	0.681
	Female	6 (50%)	3 (60%)	4 (40%)		
Residence	Rural	8 (66.7%)	3 (60%)	6 (60%)	X^2_L = 0.323	1.000
	Urban	4 (33.3%)	2 (40%)	4 (40%)		
Co-morbidities	No	10 (83.3%)	4 (80%)	6 (60%)	X^2_L = 1.455	0.244
	Asthmatic	0 (0%)	1 (20%)	4 (40%)	X^2_L = 5.578	0.026*
	Hypothyroidism	1 (8.3%)	0 (0%)	0 (0%)	X^2_L = 1.059	0.815
	Peptic ulcer	1 (8.3%)	0 (0%)	0 (0%)	X^2_L = 1.059	0.815
Seed name	Castor seed	7 (58.3%)	5 (100%)	6 (60%)	X^2_L = 0.022	1.000
	Croton seed	5 (41.7%)	0 (0.0%)	4 (40%)		
Amount	Median [IQR]	3 [2- 3]	4 [2.5 - 4.5] c	5 [3 - 6] b	Z = 8.317	0.016*
	Min - Max	1- 5	2 - 3	3 - 6		
Manner	Accidental	6 (50.0%)	5 (100%)	5 (50%)	X^2_{FFH} = 3.639	0.489
	Suicidal	2 (16.7%)	0 (0%)	2 (20%)		
	Therapeutic	4 (33.3%)	0 (0%)	3 (30%)		
Delay time	Median [IQR]	7 [1.5 - 10] c	16 [12- 48]	16 [14 - 17] a	Z = 8.333	0.016*
	Min - Max	1 - 36	6 - 48	13- 27		
Hospital stay (hours)	Median [IQR]	42 [24- 48] c	72 [55 - 72]	120 [96 - 140] a	Z = 20.011	<0.001*
	Min - Max	24- 48	55 - 96	48 - 140		

*IQR: interquartile range (25^{th} – 75^{th} percentiles); Max: maximum; Min: minimum; X^2_{FFH}: Fisher-Freeman-Halton exact test; X^2_L: Cochrane Armitage test for trend; Z: Kruskal-Wallis test; * significant at p<0.05; a: significant difference from PSS=1 on post hoc testing; b: significant difference from PSS=2 on post hoc testing; c: significant difference from PSS=3 on post hoc testing.*

Table (7): The spearman's rank-order correlation of the severity of cases with some parameters (n=27):

Parameter		Age (years)	Number of ingested seeds	Delay time (hours)	Hospital stay (hours)
Poison Severity Score (PSS)	r_s	-0.265	0.328	0.532	0.873
	p-value	0.181	0.095	0.004*	<0.001*

*r_s: coefficient of Spearman's rank-order correlation; strength of correlation: rs < ٠.3 indicate weak, rs = 0.3-0.7: moderate, rs >0.7: strong; * significant at p<0.05*

DISCUSSION

Toxic seed intoxication usually reported as sporadic cases worldwide. Too limited studies were carried on toxic seed exposure, particularly in Egypt. To our knowledge this is a novel study carried on 27 toxic seeds intoxicated cases analyzing the pattern, clinical features and outcome of intoxicated cases. The rate of toxic plants or seed ingestion is relatively low. Poison Control Center, Ain Shams University Hospitals, reported 8 plant and herbal toxicity cases in 2019 representing (0.04%) of total admitted cases **(*Abdelhamid, 2021)***. ***El-Sarnagawy et al. (2023)*** in their non-pharmacetical pediatric poisoning study at TUPCC reported 2.02% of cases with castor seeds ingestion. In order to gather reasonable number of cases, this retrospective study was carried out on data of six-year interval involving all cases of toxic seeds ingestion admitted to TUPCC from 2017 to 2022. In the current study, only 27 cases of castor and croton seeds were included (17 and10 respectively).

The majority of poisoning occurs accidentally in children. Castor seed specifically were commonly ingested by children while croton seeds were mainly used by adults for therapeutic purposes. Toxic seeds ingestion was reported to occur accidentally by unaware children who are usually attracted by the appearance of the seeds or mistaken it as candy ***(Polito et al., 2019)***.

Likely, ***Worbs et al. (2011)*** reported that major intoxications of castor seeds occurred accidentally and only a few cases intentionally used castor bean extracts in suicide attempts. Both castor and croton seeds had been used for centuries for their therapeutic properties. Castor had been used as a laxative, a remedy for abscess and baldness and for treatment of rheumatoid arthritis ***(Lim et al., 2009)***. Croton seeds also have been largely used in treating urinary tract infections, chronic constipation and infertility. Additionally, croton seeds are sometimes applied directly on the skin for treatment of arthritis, neuralgia, gout, dermatological conditions and chest infection ***(Magwilu et al., 2022)***.

Clinically, GIT manifestations including abdominal colic, diarrhea and vomiting in addition to dehydration and shock were the most evidential manifestations in both adult and pediatrics. The same results were reported by ***Lucas, (2006)*** and ***Thornton et al. (2014)***. No significant difference existed between adult or pediatrics neither between castor and croton regarding their clinical characteristics. The purgative effect of castor seeds has been attributed to the intestinal irritating effect caused by ricin ***(Battelli, 2004)***. Croton seeds contain irritating phorbol esters which has a strong laxative effect ***(Pal et al., 2014)***.

Repeated vomiting and diarrheal episodes reported in the current study of a median of six episodes explain the occurrence of dehydration, hypovolemia, and electrolyte disturbance, especially that majority of patients were pediatrics who cannot withstand severe fluid loss. Oral burning sensation was significantly reported in croton seeds mainly in adult patients. This can be explained by, the local irritating corrosive like effect that Croton has ***(Hempen and Fischer, 2009)***.

Findings of ECG in the current study revealed sinus tachycardia in about half of pediatrics, while only two children who ingested castor seeds developed sinus bradycardia. Atrial fibrillation was traced in two adults who consumed castor seeds. Bradycardia and other ECG changes were also reported in other similar cases of castor seed ingestion ***(Al-Tamimi and Hegazi, 2008)***. Rapid heart rate and bradycardia were additionally reported in the study of ***Hempen and Fischer, (2009)*** on their castor seeds intoxicated cases.

Hypotension and hypovolemia are usually compensated by the body through increasing sinus rhythm which is manifested on patients by palpitation and tachycardia ***(Kavi, 2012)***.

Ricin released from castor seeds causes inhibition of protein synthesis and inactivation of ribosomal RNA. Furthermore, ricin directly damage cell membrane and cause structural and functional changes in addition to release of inflammatory mediators leading to cellular apoptosis ***(Day et al., 2002; EFSA, 2008)***.

Extracts from croton tiglium have been proved to inhibit protein synthesis too

(Aboulthana et al., 2020). Cytotoxicity induced by ricin explains increased liver enzymes, urea and creatinine in intoxicated patients in our study. In an experimental study of ricin toxicity, blood urea levels, glutamate pyruvate transaminase, alkaline phosphatase and lactate dehydrogenase were all increased ***(Kumar et al, 2003)***.

The values of aspartate transaminase and blood urea were significantly elevated in pediatrics compared to adults would be explained by the fact that children couldn't usually withstand toxicity like adults. Hyponatremia, hypokalemia, hypoglycemia and metabolic acidosis could be attributed to repeated vomiting and diarrhea that led to electrolyte disturbance, low blood glucose and hypovolemic shock which explain acidosis ***(Grimwood and Forbes, 2009)***. Leukocytosis in about half of intoxicated cases reflects inflammatory changes produced by both toxic seeds.

On the current study, severe cases ingested significantly more number of seeds. Castor and croton toxicity is dose related and depends on the number of ingested seeds ***(Al-Tamimi and Hegazi, 2008)***.

Severe and fatal oral doses of ricin in humans have been assessed to range from 1 to 20 mg/kg (about 5 to 10 beans). It is rather difficult to calculate LD values for ricin in humans. Ricin content varies depending on the size and moisture of the seeds, cultivar, season, and plant growth stage. Besides, in poisoned patients, age, the degree of mastication, stomach content and preexisting morbidities are to be considered ***(Bradberry et al., 2003; Audi et al., 2005).***

No fatality was recorded among patients in our study and all cases were discharged improved after their management in the hospital. Meticulous supportive care is usually sufficient to manage castor and croton intoxicated cases when cases are mainly unintentional ***(Worbs et al., 2011).*** Similar cases have been successfully treated with only intensive supportive therapy ***(Nishiyama et al., 2005; Lim et al., 2009).***

Severe cases reached a hospital facility after a significantly longer median delay time than mild cases (16 and 7 hours respectively). Symptoms of intoxication arise after 3 to 20 h of castor seed ingestion ***(Worbs et al., 2011)***. In addition, lack of public knowledge about toxicity of such seeds may delay correlating the presenting complaint to the ingested seed and explains their reluctance in seeking toxicological advice. The backbone of gut decontamination is either through gastric lavage or administration of activated charcoal within one hour of a significant ingestion before absorption occurs ***(Behrman et al., 2003; Benamor et al., 2020)***. Delay in hospitalization is frequently associated with increase absorption of toxic chemicals, manifestations and severity of poisoning. In our study a moderate positive significant correlation existed between the severity of cases and the delay time to reach emergency room in hours.

The current study also revealed a strong positive significant correlation between the severity of toxicity and hospital stay in hours. Severe cases were admitted to the hospital for a significantly longer median period than mild ones. Increase severity and manifestation of toxicity usually requires more management steps which requires longer hospital stay duration. In previously reported cases of castor seed intoxication, severe cases were admitted in hospital for several days ***(Nishiyama et al., 2005; Thornton et al., 2014)***. Intensive care unit admission, intravenous fluid therapy and vasopressors were used in most severe cases to correct the resultant hypovolemia and electrolyte disturbances ***(Benamor et al., 2020)***.

CONCLUSION

Toxic seeds ingestion is not a rare problem in toxicology practice. From 2017 to 2022, twenty-seven patients were admitted to TUPCC due to castor and croton seeds ingestion. Children were mainly intoxicated accidentally while adults ingested the seeds mainly for therapeutic purposes. Manifestation of GIT disturbance, dehydration, and hypovolemia were the most relevant clinical manifestations in the studied patients. Cytotoxicity was reported in some cases manifested by increase aspartate transaminase, blood urea, electrolyte disturbance and acidosis. Increase ingested amount of seeds was associated with increase

in the severity of poisoning. Additionally, the severity of toxicity was strongly and moderately correlated to hospital stay duration and the delay time to reach emergency room respectively.

RECOMMENDATIONS

The authors recommend a multi-centers study of toxic seeds ingestion to report any unusual findings and unfavorable prognosis. Study of toxic plants or seed toxicity would help in updating the management protocols and improve the outcomes. Increasing the public awareness of accidental poisoning with toxic plants and their harmful effects, especially those who ingest seeds for therapeutic issues could help minimizing the risk of exposure. Knowledge about toxic plant types should be spread within the population in general and to children caregivers in particular.

Author contributions

Nadia E. Helal contributed to the conception, design, material preparation, data collection, analysis and revision of the final manuscript. Sohair F. Hasn contributed in data collection and data entry. Samah M. Elbastawesy contributed in data analysis, methodology writing and final manuscript revision and editing.

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النمط والسمات السريرية والنتائج العلاجية الناتجة فى حالات تناول بذور الخروع والكروتون: دراسة إسترجاعية لمدة ست سنوات في مركز طنطا الجامعي لعلاج حالات التسمم

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الملخص العربي

المقدمة: إكتسب إستخدام الأدوية العشبية لعلاج المشاكل الصحية إهتماما كبيرا على مدار سنوات عديدة. تعرف بذور الخروع والكروتون بقيمتها العلاجية، ومع ذلك، يمكن أن يؤدي إبتلاعها إلى حدوث حالات تسمم و يمكن حتى أن تؤدى للوفاة.

الهدف من الدراسة: هدفت هذه الدراسة الإسترجاعية إلى دراسه النمط والسمات السريرية والنتائج العلاجية لحالات تناول بذورالخروع والكروتون التي تم دخولها إلى مركز طنطا الجامعي لعلاج حالات التسمم.

تصميم الدراسة: شملت هذه الدراسة ٢٧ حالة من تناول بذور الخروع أو الكروتون من بداية عام ٢٠١٧ حتى نهاية عام ٢٠٢٢. تم تسجيل جميع البيانات الديموغرافية والسريرية والمختبرية للحالات قيد الدراسة. بالإضافة إلى ذلك ، تم تسجيل النتائج العلاجية لجميع الحالات.

النتائج: الغالبية العظمى من المرضى (٦٣٪) كانوا أطفالًا تعرضوا للتسمم عرضيا ببذور الخروع، على عكس معظم البالغين الذين ابتلعوا بذور الكروتون لأغراض علاجية. وبشكل عام، كانت أعراض اعتلال الجهاز الهضمي كالقئ والإسهال والمغص والجفاف هي الأكثر شيوعا. وارتبط إبتلاع بذور الكروتون بشكل كبير بالإحساس بحرقان في الفم والبلعوم. وتم رصد ارتفاع ملحوظ لأنزيم الأسبارتات ترانساميناز واليوريا في حالات الأطفال. وتم أيضا رصد ارتفاعا في عدد كرات الدم البيضاء ، واضطراب فى مستويات الصوديوم والبوتاسيوم بالدم ، وحامضية الدم ، بالاضافة الى انخفاض مستوى السكر في الدم، وارتفاع مستوى إنزيم الكرياتينين فوسفوكيناز. وقد أظهر ابتلاع بذور الخروع المزيد من الإنحرافات في تخطيط القلب الكهربى . وبشكل عام، تم نقل ٣٣.٣٪ من المرضى إلى وحدة العناية المركزة، ومع ذلك، أظهرت جميع الحالات قيد الدراسة نتائج علاجية إيجابية.

الخلاصة: يؤدي ابتلاع المزيد من بذورالخروع والكروتون إلى زيادة شدة االتسمم. وكذلك ارتبطت شدة التسمم فى المرضى بشكل كبير بمدة البقاء في المستشفى وطول الفاصل الزمني ما بين تناول البذور والوصول إلى المنشأة الصحية.

التوصيات: يعتبر أفضل طريقة للوقاية من تناول بذور الخروع والكروتون السامة هي زيادة الوعي العام لدى الجمهورعن النباتات السامة والضارة ، وخاصة عند مقدمي الرعاية للأطفال.