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Correlation between theophylline level and troponin I versus kinase-MB as predictor markers of the severity and outcomes in acute theophylline toxicity in adults

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Abstract

Background: Theophylline, a methylxanthine, remains commonly used in several countries to manage both acute and chronic bronchial asthma. It remains popular due to its effectiveness, affordability, and widespread availability. Acute theophylline toxicity remains a significant hazard, due to the absence of a specific antidote. There is a significant need to predict the severity and outcomes of patients with acute theophylline poisoning to guide appropriate treatment. **Methods:** This prospective cohort study included 34 patients admitted to the Poison Control Center at Ain Shams University Hospitals (PCC-ASUH) over a 6-month period from January to June 2022 with a history of acute theophylline poisoning. Troponin I and creatine kinase-MB levels were assessed at 6 and 12 hours after admission. **Results** showed that troponin I levels at 6 and 12 hours post ingestion, along with creatine kinase-MB levels at 12 hours, were significantly elevated in patients with severe acute theophylline poisoning and in those who required intensive care unit admission and hemodialysis. **Conclusion:** Troponin I can predict severity, need for ICU admission, and hemodialysis in acute theophylline poisoning regardless of early or delayed presentation, while CK-MB may serve as a predictor in patients presenting late. **Recommendation:** Troponin recommended as a predictor of severity in acute intoxicated patients in early and delayed presentation. CKMB use as a predictor of severity in acute intoxicated patients in delayed presentation.

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Key words Theophylline; Acute poisoning; Troponin I; Creatine kinase-MB; cardiotoxicity

Introduction

Theophylline is a methylxanthine used for the treatment of respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD) and apnea of prematurity, due to its pharmacological action in smooth muscle relaxation, anti-inflammatory properties and powerful stimulation of the central nervous system (CNS) respiratory center (Kong et al., 2021).

Theophylline toxicity occurs when serum theophylline levels exceed the therapeutic range. This can occur by intentional overdose or unintentionally when metabolism and/or clearance of theophylline is altered due to certain physiological stressors (Journey & Bentley, 2021).

Theophylline intoxication may be acute, acute on therapeutic or chronic, both intentional and accidental toxicity are common due to its wide availability (Abuelfadl et al., 2017)

Acute theophylline poisoning involves gastrointestinal symptoms, neurologic effects like seizures, musculoskeletal manifestations such as muscle contractions, and cardiovascular complications including tachycardia and arrhythmias. These symptoms can escalate rapidly, leading to life-threatening events like refractory seizures and cardiac arrest that may be resistant to standard treatments (Khalifa and Lashin, 2018).

The exact mechanism of cardiac toxicity is still unclear. However, it might be attributed to increased circulating catecholamines and/or to cardiac adenosine receptors antagonism (Abuelfadl et al., 2017).

Cardiovascular complications represent a major contribution for morbidity and mortality in cases with acute theophylline intoxication as focal necrosis and subendocardial myolysis, cardiac dysrhythmia of theophylline intoxication was associated with new onset of myocardial ischemia. Moreover, autopsy findings in asthmatic patients with methylxanthines therapy revealed multiple areas of myocardial necrosis (Hodeib & Ghonem, 2019).

Theophylline and its derivatives have been associated with elevated troponin as well as myocardial infarction in patients without coronary artery disease (Cashy et al., 2020).

There are no antidotes to reverse the toxic effects of theophylline; therefore, therapy is focused on enhancing its elimination. In acute overdose, gastric decontamination with multi-dose activated charcoal (MDAC) is initially recommended if the patient is able to protect the airway (Kong et al., 2021).

This study aims at:

Investigating the potential benefit of troponin I and CK-MB as early markers of severity and outcomes induced by acute theophylline toxicity.

Patients and Methods

The current study was prospective cohort study conducted on patients admitted to (PCC-ASUH) for 6 months duration from January 2022 to June 2022 with a history of acute exposure to theophylline toxicity.

Grouping:

1. Control Group: -

34 healthy volunteers aged 18 years or more, of both sexes, were selected with no history of any medical diseases or toxic exposure.

2. Patient Group: -

34 patients, aged 18 years or more, of both sex, with acute theophylline toxicity within 6 hours of ingestion, were subjected to blood sampling at 6- and 12-hours post-ingestion for measurement of troponin I and CKMB. and after that classified according to (Murray et al., 2011) based on their serum theophylline levels (therapeutic range 10–20 mg/L) in to :-

- Mild group toxicity: serum theophylline levels ranging from 20 to 40 mg/L.
- Moderate group toxicity: serum theophylline levels ranging from 40 and 80 mg/L.
- Severe group toxicity: serum theophylline levels ranging from 80 to 100 mg/L.

Patients with any of the following criteria were excluded from the current study: Co-ingestion of other medications or xenobiotics, Pre-existing diseases such as cardiac diseases, hypertension, diabetes mellitus and both hepatic and renal diseases, associated trauma, special habits as smoking. Those who received any medications before presenting to PCC-ASUH.

Ethical considerations:

An official permission was taken from the general director of the PCC-ASUH. Approval was obtained from the Local Research Ethics Committee at the faculty of medicine, ASU. (FWA 000017585-approval no FMASU MS 8/2021). An informed valid consent was taken from patients' legal guardians. All personal data were kept anonymous to ensure confidentiality of records.

Study methods:

History taking and clinical examination were done for the included patients; data were collected and recorded in a special sheet including:

- Sociodemographic data (age & gender) & Intoxication data (type and amount of ingested theophylline by history, mode of poisoning, delay time).
- Detailed clinical examination (including general and local) done on admission and 6 hours after and repeated every 12 hours for ICU patients and every 24 hours for those in the inpatient ward until discharge.
- Investigations:
  A. All biological samples withdrawn 6 hours post ingestion; troponin I and CKMB repeated 12 hours post ingestion, Venous blood sample (3 ml) were taken from each patient under complete sterile conditions by a plastic disposable syringe, centrifuged for 5 minutes with Jouan centrifuge at rate of 5000c/min to collect serum and arterial blood sample (1ml) for arterial blood gas analysis (ABG). Immediate analysis of the following parameters. (Theophylline level, Troponin I, CK-MB, ABG, Serum Potassium level, Random Blood Glucose)
  B. Electrocardiography (ECG).
- Outcome: - The outcomes of the Patients involved in this study were recorded regarding the following:
  A. Mortality.
  B. Morbidity: ICU admission, any organ failure, need for supportive treatment to any complications (e.g. shock, ARDS), hemodialysis or mechanical ventilation.
  C. Hospital stay.

Data management and Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013.IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using mean, standard deviation for non-normally distributed data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level.

Results

The study included 34 patients with acute theophylline poisoning who fulfilled the eligibility criteria during the study period.

In this study mild case constituted 35.3%, moderate cases accounted for 41.2%, while severe cases represented only 23.5%.

Table (1) regarding sociodemographic data, by using one-way ANOVA test the mean age in both severe and moderate groups was higher than that in the mild group. Females were predominant in acute theophylline toxicity, with no significant difference observed among mild, moderate, and severe groups using chi square test.

Concerning intoxication data (table 1), one-way ANOVA test showed that the mean delayed hours were higher in moderate and severe cases compared to mild cases. The chi-square test revealed that suicide was the most prevalent manner of poisoning. Among severe cases (62.5%) were intoxicated by sustained-release preparations, while (37.5%) were intoxicated by conventional theophylline preparations. In mild cases, sustained release was equal to conventional and there was no significant difference between intoxication data and studied groups.

Acute toxicity was more common than acute-on-top chronic toxicity, and there was no significant difference between the mild, moderate, and severe groups.

Vital data results indicate that almost all patients were tachycardic and tachypneic. Most patients were normotensive, while (8.8%) of cases were hypertensive and (5.9%) of cases were hypotensive.

ANOVA test showed significant differences in pulse rate among the mild, moderate, and severe groups. In post hoc test pulse rates found to be significantly different between mild and moderate as well as between mild and severe groups. However,

there is no statistically significant difference in pulse rates between moderate and severe groups (table 1).

According to the chi-square test results in Table (2) palpitation representing (25%) of mild cases and (28.6%) of moderate cases. Chest pain appeared in only (7.1%) of the moderate cases, while shock was present in (7.1%) of the mild cases and (12.5%) of the severe cases. Cardiac arrest was found in one case in the severe group. There is no significant difference between cardiovascular manifestation among the studied groups.

Regarding gastrointestinal manifestations, most patients experienced nausea and vomiting. Approximately (62.5%) of severe cases had epigastric pain, and half of them had hematemesis. There is no significant difference between gastrointestinal manifestation among studied groups.

Concerning neurological manifestations, convulsions represented (25%) of severe cases, and agitation was present in (100%) of severe cases. Additionally, the p-values are less than 0.05, suggesting a statistically significant association between the variables (agitation and convulsion) and the groups being compared.

Table (3), potassium levels indicate that hypokalemia was present in (58.8%) of mild cases, (41.7%) of moderate cases, and (71.4%) of severe cases. The result of the one-way ANOVA indicates significant differences in potassium levels among the mild, moderate, and severe groups.

In post hoc test potassium levels are significantly different between the mild group and both the moderate and severe groups. However, there is no significant difference between the moderate and severe groups.

The random blood glucose findings indicate that hyperglycemia was present in (61.8%) of mild cases, (25%) of moderate cases, and (71.4%) of severe cases. One-way ANOVA revealed significant differences in random blood glucose levels among the mild, moderate, and severe groups. The mild group has the lowest mean random blood glucose level, while the severe group has the highest mean, suggesting a gradient of severity. There are significant differences in post-hoc analyses, especially between the (mild and severe groups), (moderate and severe group).

Concerning CK-MB levels at 6 -and 12- hours post-ingestion, the Kruskal-Wallis test indicates a statistically significant variation in CK-MB levels among the three groups (mild, moderate, and severe). The decreasing p-values from 6 to 12 hours post-ingestion suggests that increasing significance in CK-MB levels among severity groups.

After conducting post-hoc analyses, the CKMB level at 6 hours post ingestion, the differences are most pronounced between the mild and severe group, CKMB level at 12 hours post ingestion show significant post-hoc analyses, between mild and moderate groups, and between mild and severe groups

In the analysis of troponin I levels at both 6 and 12 hours post ingestion, there are significant differences indicating a gradient of severity among the mild, moderate, and severe groups.

The post-hoc analyses reveal that troponin I level measured 6 hours after ingestion, the differences are most pronounced between the mild and moderate groups, as well as between the mild and severe groups. Additionally, the troponin I level at 12 hours post ingestion show highly significant post-hoc analyses, between mild and moderate group, between mild and severe group, and between moderate and severe group.

The chi-square test showed that compensated respiratory alkalosis was the most frequent ABG disturbance in all groups. Metabolic acidosis appeared more often in severe cases, indicating greater severity. There was a significant association between ABG patterns and the severity of intoxication.

Table (4) show the mortality rate was 1 out of 34 cases, representing (2.5%) of all cases and (12.5%) of severe cases.

Regarding the site of admission, shows that (21.4%) of moderate cases required ICU admission, while all severe cases were admitted to the ICU. The result of the Chi-square test revealed a significant difference between mild, moderate, and severe cases.

As for the hospital stays, Kruskal-Wallis test showed a significant differences exist in the durations of hospital stays among the studied groups, with longer stays associated with higher severity.

The post hoc analyses further interpret these differences, revealing that the hospital stay in the mild group is significantly different from both the moderate and severe groups. Additionally, the moderate group exhibits a significant difference in hospital stays compared to the severe group.

The chi-square test showed that 20.6% of cases required hemodialysis, all of which were from the severe group. There was a significant association between the need for hemodialysis and case severity

The Mann-Whitney test in Table (5) showed that patients who underwent hemodialysis had significantly higher CKMB levels and troponin levels at both 6 and 12 hours post-ingestion compared to those who did not.

Similarly, for the site of admission, CKMB levels and troponin I at 6- and 12- hours post ingestion is significantly higher in patients admitted to the ICU compared to those admitted inward.

The decreasing p-values from 6 to 12 hours post-ingestion in both hemodialysis and ICU admission indicate an increasing significance, suggesting that CKMB and troponin I levels become more specific over time in distinguishing patients in need of hemodialysis, as well as distinguishing between patients admitted to the ICU and those who were not.

In Table (6), figure (3 to 6) Spearman correlation analysis showed a significant positive correlation between CKMB levels at both 6- and 12-hours and Troponin I level at both 6- and 12-hours post ingestion with the duration of hospital stays. These relationships are statistically significant, suggesting that monitoring CKMB and troponin I levels may provide valuable information about the potential length of hospitalization.

Table (7) shows that the Mann-Whitney test demonstrate a significant difference in Troponin I levels at 6- and 12- hours post ingestion, as well as CKMB levels only at 12 hours post ingestion, between the control and patient groups. Conversely, there is no statistically significant difference in CKMB levels at 6 hours post-ingestion between the two groups.

Table (8) show receiver operating characteristic (ROC) curve analysis. (figure 1) using a cut-off point of >0.03 for Troponin levels at 6- hours post ingestion provides a diagnostic tool with a good balance between sensitivity and specificity. It is highly specific (100%), correctly identifying all true negatives, and moderately sensitive (67.65%) in identifying the true positives. Troponin I at 6- hours post ingestion appears to be a promising biomarker for predicting severe cases of acute theophylline toxicity.

Also show that Troponin I level at 12- hours (figure 2) with a cut-off value >0.03 and CKMB level at 12 hours, with a cut-off value of ≥ 10.1.

Troponin I at 12 hours post ingestion has higher sensitivity (85.29%) compared to CKMB at 12 hours post ingestion (61.76%), indicating a better ability to correctly identify patient with the acute theophylline toxicity. Moreover, the specificity of troponin I at 12 hours post ingestion 100% means there are no false positives. while specificity of CKMB at 12 hours 94.12% indicates that there is a 5.88% chance of false positives that mean troponin I, when elevated at 12 hours, is highly specific for severe theophylline toxicity.

Both tests have high positive predictive values (+PV), suggesting that patient with positive test results are likely to have toxicity. Troponin I at 12 hours post ingestion has a higher negative predictive value (-PV) of 87.2% compared to CKMB (71.1%), indicating a better ability to correctly identify patient without toxicity.

Table 1: Comparison of Socio-demographic, Intoxication, and Vital Signs Data Among 34 Patients Classified as Mild, Moderate, or Severe on Admission

		Patients group	**Mild**	**Moderate**	**Severe**	**Test value**	**P-value**	
		No. = 34	**No. = 12**	**No. = 14**	**No. = 8**			
Socio-demographic data								
Age	Mean ±SD	25.44 ± 11.8	20.58 ± 6.01	25.71 ± 8.93	32.25 ± 18.92	2.578•	P=0.092	
	Range	18 – 76	18 – 39	18 – 42	19 – 76			
Sex	Female	28 (82.4%)	10 (83.3%)	10 (71.4%)	8 (100%)	2.872*	P=0.238	
	Male	6 (17.6%)	2 (16.7%)	4 (28.6%)	0 (0%)			
Intoxication data								
Mode	Suicidal	34 (100.0%)	12 (100%)	14 (100%)	8 (100%)	NA	NA	
Route	Oral	34 (100.0%)	12 (100%)	14 (100%)	8 (100%)	NA	NA	
Delay hour	Mean ±SD	4.32 ± 1.98	4 ± 2	4.36 ± 2.1	4.75 ± 1.91	0.334•	P=0.719	
	Range	1 – 6	1 – 6	1 – 6	1 – 6			
Type of preparation	Conventional	18 (52.9%)	6 (50%)	9 (64.3%)	3 (37.5%)	1.531*	P=0.465	
	SR	16 (47.1%)	6 (50%)	5 (35.7%)	5 (62.5%)			
Type of toxicity	Acute	25 (73.5%)	10 (83.3%)	10 (71.4%)	5 (62.5%)	1.124*	P=0.570	
	Acute on Chronic	9 (26.5%)	2 (16.7%)	4 (28.6%)	3 (37.5%)			
Vital data								
Pulse rate	Mean ± SD	107.59±18.51	91.75 ± 13.86	112.43 ± 18.05	122.88 ± 24.62	7.623•	P=0.002	
							Mild Vs moderate	**0.008**
	Range	68 –173	68 – 110	90 – 158	100 – 173		**Mild Vs severe**	**0.001**
							Moderate Vs severe	**0.212**
Pulse	Bradycardia	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)	1.082*	P=0.582	
	Normal	13 (38.2%)	5 (41.7%)	4 (28.6%)	4 (50%)			
	Tachycardiac	21 (61.8%)	7 (58.3%)	10 (71.4%)	4 (50%)			
Blood pressure	Hypotensive	2 (5.9%)	0 (0%)	1 (7.1%)	1 (12.5%)	5.607*	P=0.230	
	Normal	29 (85.3%)	12 (100%)	12 (85.7%)	5 (62.5%)			
	Hypertensive	3 (8.8%)	0 (0%)	1 (7.1%)	2 (25%)			
Temperature	Hypothermia	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)	1.472*	P=0.479	
	Normal	33 (97.1%)	12 (100%)	13 (92.9%)	8 (100%)			
	Hyperthermia	1 (2.9%)	0 (0%)	1 (7.1%)	0 (0%)			
Respiratory rate	Bradypneic	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)	0.070*	P=0.966	
	Normal	5 (14.7%)	2 (16.7%)	2 (14.3%)	1 (12.5%)			
	Tachypneic	29 (85.3%)	10 (83.3%)	12 (85.7%)	7 (87.5%)			

P-value > 0.05: Non-significant; P-value < 0.05: Significant, *: Chi-square test; •: One Way ANOVA,. SD: standard deviation, SR: slow release.

Table 2: Comparison of Clinical Manifestations Among 34 Patients Classified as Mild, Moderate, or Severe on Admission.

Clinical manifestations		Patients group	Mild	Moderate	Severe	Test value	P-value
		No. = 34	No. = 12	No. = 14	No. = 8		
Cardiovascular system (CVS)							
Chest pain	No	33 (97.1%)	12 (100%)	13 (92.9%)	8 (100%)	1.472*	P=0.479
	Yes	1 (2.9%)	0 (0%)	1 (7.1%)	0 (0%)		
Palpitation	No	27 (79.4%)	9 (75%)	10 (71.4%)	8 (100%)	2.763*	P=0.251
	Yes	7 (20.6%)	3 (25%)	4 (28.6%)	0 (0%)		
Cardiac arrest	No	33 (97.1%)	12 (100%)	14 (100%)	7 (87.5%)	3.348*	P=0.187
	Yes	1 (2.9%)	0 (0%)	0 (0%)	1 (12.5%)		
Shock	No	32 (94.1%)	12 (100%)	13 (92.9%)	7 (87.5%)	1.423*	P=0.491
	Yes	2 (5.9%)	0 (0%)	1 (7.1%)	1 (12.5%)		
Gastrointestinal tract (GIT)							
Nausea	No	2 (5.9%)	1 (8.3%)	0 (0%)	1 (12.5%)	1.638*	P=0.441
	Yes	32 (94.1%)	11 (91.7%)	14 (100%)	7 (87.5%)		
Vomiting	No	2 (5.9%)	1 (8.3%)	0 (0%)	1 (12.5%)	1.638*	P=0.441
	Yes	32 (94.1%)	11 (91.7%)	14 (100%)	7 (87.5%)		
Hematemesis	No	26 (76.5%)	11 (91.7%)	11 (78.6%)	4 (50%)	4.690*	P=0.096
	Yes	8 (23.5%)	1 (8.3%)	3 (21.4%)	4 (50%)		
Melena	No	34 (100.0%)	12 (100%)	14 (100%)	8 (100%)	NA	NA
	Yes	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)		
Epigastric pain	No	21 (61.8%)	8 (66.7%)	10 (71.4%)	3 (37.5%)	2.670*	P=0.263
	Yes	13 (38.2%)	4 (33.3%)	4 (28.6%)	5 (62.5%)		
Others	No	30 (88.2%)	10 (83.3%)	12 (85.7%)	8 (100%)	3.184*	P=0.527
	Colic	3 (8.8%)	2 (16.7%)	1 (7.1%)	0 (0%)		
	Diarrhea	1 (2.9%)	0 (0%)	1 (7.1%)	0 (0%)		
Central nervous system (CNS)							
Irritability	No	10 (29.4%)	6 (50%)	4 (28.6%)	0 (0%)	5.788*	P=0.055
	Yes	24 (70.6%)	6 (50%)	10 (71.4%)	8 (100%)		
Tremors	No	34 (100.0%)	12 (100%)	14 (100%)	8 (100%)	NA	NA
	Yes	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)		
Agitation	No	23 (67.6%)	12 (100%)	11 (78.6%)	0 (0%)	23.230*	P=0.000
	Yes	11 (32.4%)	0 (0%)	3 (21.4%)	8 (100%)		
Convulsion	No	32 (94.1%)	12 (100%)	14 (100%)	6 (75%)	6.906*	P=0.032
	Yes	2 (5.9%)	0 (0%)	0 (0%)	2 (25%)		

P-value > 0.05: Non-significant; P-value < 0.05: Significant, *: Chi-square test

Table 3: Comparison of Laboratory Parameters Among 34 Patients Classified as Mild, Moderate, or Severe on Admission.

		Patients group	Mild	Moderate	Severe	Test value	P-value	
		No. = 34	No. = 12	No. = 14	No. = 8			
Potassium	Hypokalemia	0 (0.0%)	20 (58.8%)	5 (41.7%)	10 (71.4%)	4.729*	P= 0.316	
	Normal	34 (100.0%)	13 (38.2%)	7 (58.3%)	3 (21.4%)			
	Hyperkalemia	0 (0.0%)	1 (2.9%)	0 (0%)	1 (7.1%)			
Potassium Level mEq/L	Mean ± SD	3.33 ± 0.56	3.84 ± 0.56	3.14 ± 0.24	2.89 ± 0.41	14.943•	0.000	
							Mild vs Moderate	**0.000**
	Range	2.5 –5.3	3.4 – 5.3	2.6 – 3.5	2.5 – 3.5		**Mild vs Severe**	**0.000**
							Moderate vs Severe	**0.177**
Random blood sugar	Normal	34 (100.0%)	13 (38.2%)	9 (75%)	4 (28.6%)	12.374*	P= 0.002	
	Hyperglycemia	0 (0.0%)	21 (61.8%)	3 (25%)	10 (71.4%)			
Random blood Sugar mg/dl	Mean ± SD	171.64± 60.05	131.67 ± 29.11	166.86 ± 50.34	240.00 ± 53.28	14.190•	**P= 0.000**	
							Mild vs Moderate	**0.055**
	Range	74– 322	83 – 182	74 – 238	168 – 322		**Mild vs Severe**	**0.000**
							Moderate vs Severe	**0.001**
CKMB u/L (6hrs)	Median (IQR)	12.66(8.6–18)	9.15 (7.5 – 12.9)	14.25 (9.2 - 18)	21.9(12.05 - 59)	7.698‡	**P = 0.021**	
							Mild vs Moderate	**0.150**
	Range	0.9 – 211	0.9 – 22.7	4.5 – 211	11.9 – 123		**Mild vs Severe**	**0.004**
							Moderate vs Severe	**0.172**
CKMB u/L (12hrs)	Median (IQR)	18.8(15.3 – 25.1)	14.9 (12.8 – 17.6)	19 (16.7 – 25.1)	25.6 (21.4 – 123.5)	13.361‡	**P = 0.001**	
							Mild vs Moderate	**0.006**
	Range	10.1 – 444	10 – 20	13.5 – 240	15.1 – 444		**Mild vs Severe**	**0.002**
							Moderate vs Severe	**0.101**
Troponin. I ng/ml (6hrs)	Median (IQR)	0.06 (0.02 – 0.1)	0.02 (0.01 - 0.04)	0.07 (0.06 - 0.1)	0.14 (0.04 - 0.71)	12.992‡	**P = 0.002**	
							Mild vs Moderate	**0.000**
	Range	0.01 – 12	0.01 – 0.07	0.03 – 0.5	0.01 – 12		**Mild vs Severe**	**0.031**
							Moderate vs Severe	**0.495**
Troponin. I ng/ml (12 hrs)	Median (IQR)	0.09 (0.06 – 0.28)	0.05 (0.02 - 0.07)	0.1 (0.09 - 0.28)	0.99 (0.22 - 1.29)	22.364‡	**P = 0.000**	
							Mild vs Moderate	**0.000**
	Range	0.01 – 14	0.01 – 0.09	0.02 – 0.9	0.14 – 14		**Mild vs Severe**	**0.000**
							Moderate vs Severe	**0.004**
Arterial blood Gases (ABG)	Normal	9(26.5%)	6 (50%)	3 (21.4%)	0 (0%)	17.604*	P=0.024	
	Metabolic acidosis	7(20.6%)	0 (0%)	2 (14.3%)	5 (62.5%)			
	Respiratory alkalosis	3 (8.8%)	2 (16.7%)	1 (7.1%)	0 (0%)			
	Compensated metabolic acidosis	2 (5.9%)	1 (8.3%)	1 (7.1%)	0 (0%)			
	Compensated respiratory alkalosis	13(38.2%)	3 (25%)	7 (50%)	3 (37.5%)			

P-value > 0.05: Non-significant; P-value < 0.05: Significant, *: Chi-square test; •: One Way ANOVA; ‡: Kruskal-Wallis test.

Table 4: Comparison of Outcomes Among 34 Patients Classified as Mild, Moderate, or Severe on Admission.

Out come		Patients group	Mild	Moderate	Severe	Test value	P-value	
		No. = 34	No. = 12	No. = 14	No. = 8			
Mortality	No	33(97.1%)	12 (100%)	14 (100%)	7 (87.5%)	3.348*	P=0.187	
	Yes	1 (2.9%)	0 (0%)	0 (0%)	1 (12.5%)			
Site of admission	Inward	23(67.6%)	12 (100%)	11 (78.6%)	0 (0%)	23.230*	P=0.000	
	ICU	11(32.4%)	0 (0%)	3 (21.4%)	8 (100%)			
Hospital stays (days)	Median (IQR)	2 (1 – 3)	1 (1 - 1.5)	2 (1 – 3)	3 (3 - 9.5)	15.055‡	P = 0.001	
							Mild vs Moderate	**0.044**
	Range	1 –20	1 – 3	1 – 8	2 – 20		**Mild vs Severe**	**0.000**
							Moderate vs Severe	**0.009**
Hemodialysis	No	27(79.4%)	12 (100%)	14 (100%)	1 (12.5%)	28.648*	P=0.000	

P-value > 0.05: Non-significant; P-value < 0.05: Significant, *: Chi-square test; ‡: Kruskal-Wallis test, ICU: intensive care unit

Table 5: Comparison of CK-MB and Troponin I Levels at 6 and 12 Hours Post-Ingestion and Outcomes Among 34 Patients.

		CKMB u/L (6hrs)	Test value	P-value	CKMB u/L (12hrs)	Test value	P-value	TROP. I ng/ml (6hrs)	Test value	P-value	TROP. I ng/ml (12 hrs)	Test value	P-value
		Median (IQR)			Median (IQR)			Median (IQR)			Median (IQR)		
Hemo-dialysis	No	11 (8-16.2)	-2.216•	0.027	17 (14.8-19.8)	-3.174•	0.002	0.05 (0.02-0.07)	-2.321•	0.020	0.08 (0.04-0.11)	-3.642•	0.000
	Yes	28.9 (12.5-59)			26 (24.4-132.5)			0.15 (0.06-1.2)			1.17 (0.28- 1.3)		
	Yes	39.5 (18- 61)			237. (30 – 444)			6.25 (0.5-12)			7.45 (0.9-14)		
Site of admission	Inward	10 (7.5-14.7)	-3.093•	0.002	17 (14-19)	-3.590•	0.000	0.05 (0.02-0.07)	-2.338•	0.019	0.08 (0.04-0.09)	-4.400•	0.000
	ICU	18 (13.5-59)			26 (22-132.5)			0.13 (0.06-0.5)			0.8 (0.28-1.28)		

P-value > 0.05: Non-significant; P-value < 0.05: Significant, •: Mann-Whitney test, ICU: intensive care unit.

Table 6: Comparison Between CK-MB and Troponin I Levels at 6 and 12 Hours Post-Ingestion and Hospital Stay Among the 34 Studied Patients.

Outcome	CKMB u/L (6hrs)		CKMB u/L (12hrs)		TROP. I ng/ml (6hrs)		TROP. I ng/ml (12 hrs)	
	R	P-value	r	P-value	r	P-value	r	P-value
Hospital stays (days)	0.524**	0.001	0.654**	0.000	0.467**	0.003	0.641**	0.000

P-value > 0.05: Non-significant; P-value < 0.05: Significant, Spearman correlation coefficient

Table 7: Comparison Between Control Group and Patient Group (n = 34) in Troponin I and CK-MB Levels.

		Control group	Patients group	Test value	P-value
		No.=34	No.=34		
CKMB level u/L (6hrs)	Median (IQR)	15.7 (12.3 – 21.2)	12.66(8.6– 18)	-1.908‡	0.342
	Range	8.8 – 26	0.9 – 211		
CKMB level u/L (12hrs)	Median (IQR)	15.7 (12.3 – 21.2)	18.8(15.3 – 25.1)	-2.177‡	0.003
	Range	8.8 – 26	10.1 – 444		
TROP. I level ng/ml (6hrs)	Median (IQR)	0.02 (0.01 - 0.02)	0.06 (0.02 - 0.1)	-4.678‡	0.000
	Range	0.01 – 0.03	0.01 – 12		
TROP. I level ng/ml (12 hrs)	Median (IQR)	0.02 (0.01 – 0.02)	0.09 (0.06 – 0.28)	-6.520‡	0.000
	Range	0.01 – 0.03	0.01 – 14		

P-value > 0.05: Non-significant; P-value < 0.05: Significant, ‡: Mann-Whitney test, IQR: interquartile range

Table 8: Validity of troponin I and CKMB in prediction severe cases

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
Troponin level at 6 hours (ng/ml)	>0.03	0.825	67.65	100.00	100.0	75.6
Troponin level at 12 hours (ng/ml)	>0.03	0.941	85.29	100.00	100.0	87.2
CKMB level 12 hours (u/L)	≥ 10.1	0.708	61.76	94.12	91.3	71.1

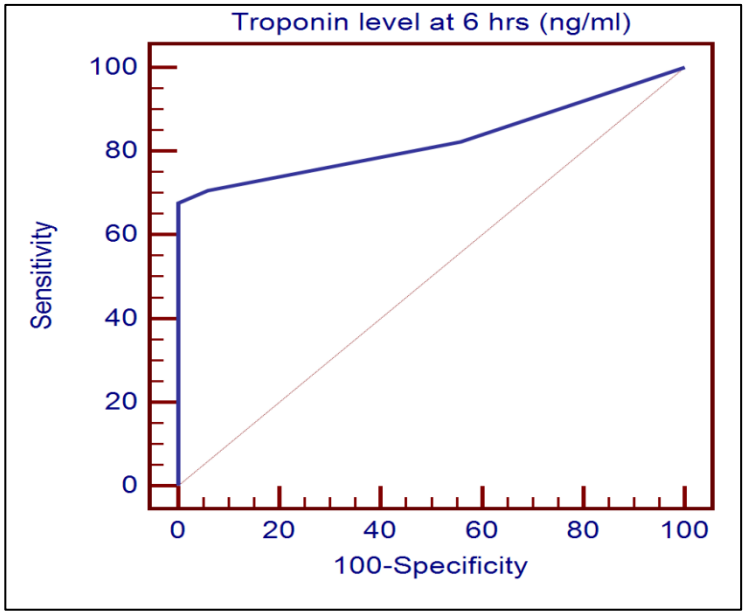

Fig.1: ROC curve to assess Troponin I level 6 hours post ingestion to detect diseased group.

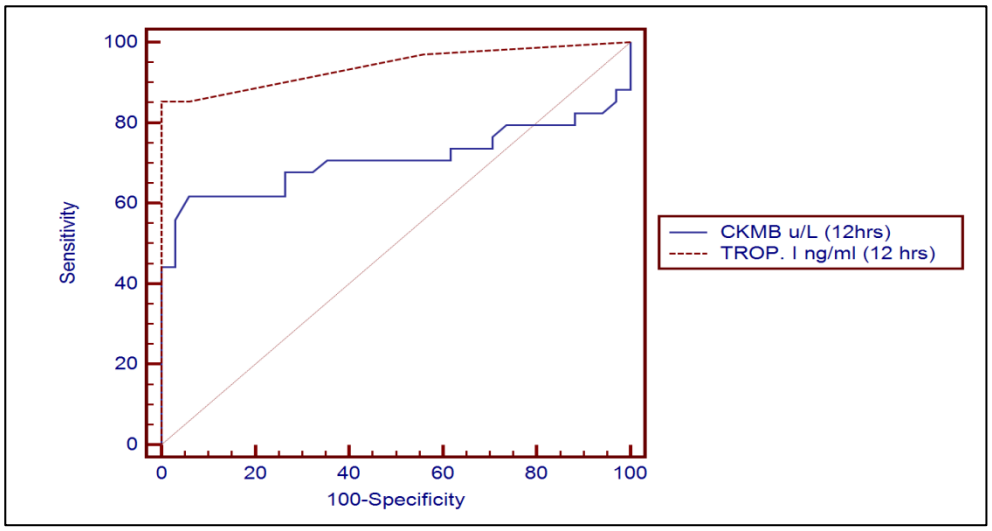

Fig. 2: ROC curve to assess Troponin I level 12hrs post ingestion and CKMB level 12 hours post ingestion to detect diseased group.

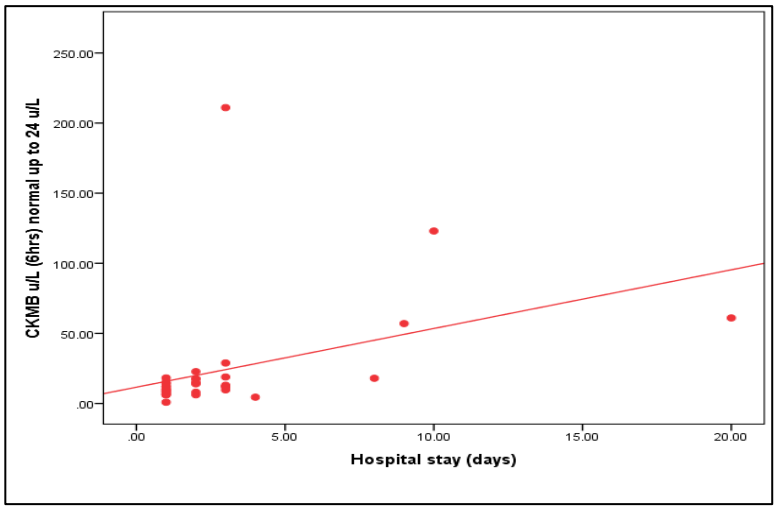

Fig. 3: Correlation of CKMB at 6 hours post-ingestion with Hospital stay (days).

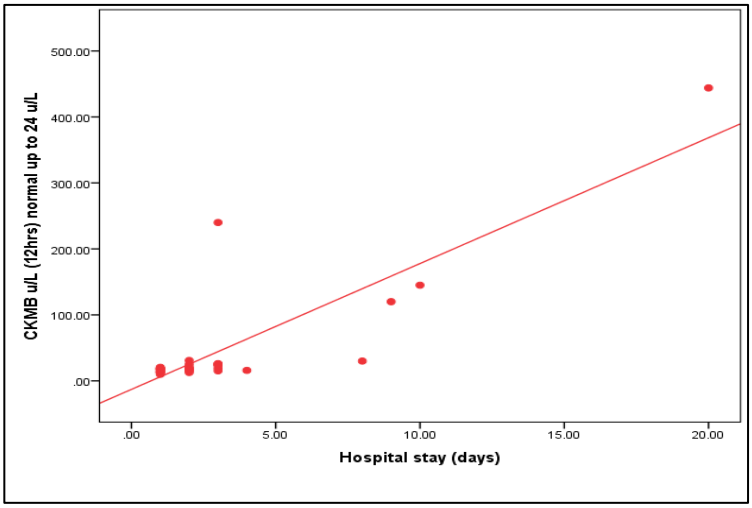

Fig. 4: Correlation of CKMB at 12 hours post-ingestion with Hospital stay (days).

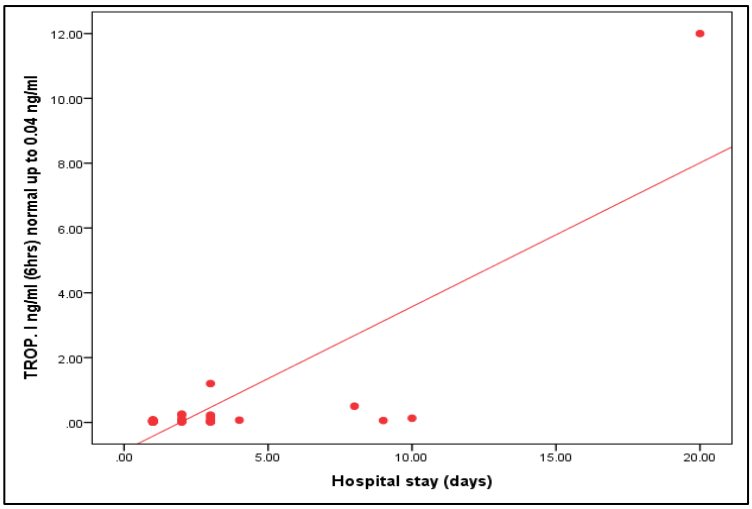

Fig.5: Correlation of Troponin I 6 hours post-ingestion with hospital stay (days)

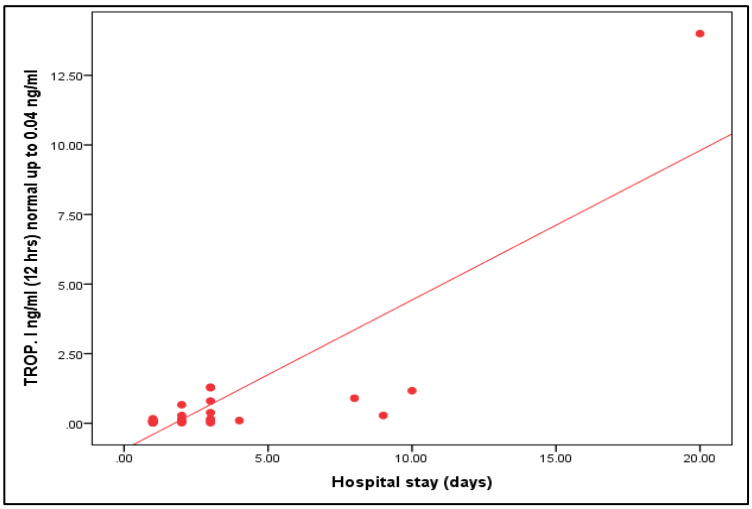

Fig. 6: Correlation of Troponin I 12 hours post-ingestion with hospital stay (days)

Discussion

Theophylline; a natural ingredient of tea and cocoa plants, is widely used as bronchodilator for the treatment of asthma and chronic obstructive pulmonary disease (COPD) due to its cheap price. Additionally, it is used as an anti-inflammatory, diuretic, smooth muscle relaxant, and also stimulant to respiratory, nervous and cardiac systems (Abdelwahab and Hussien, 2020).

Methylxanthine cardiotoxicity results from several complex pathways. Phosphodiesterase inhibition and adenosine receptor antagonism alone do not explain all its cardiac effects (Sharif et al., 2023).

Methylxanthines also act as cardiac stimulants, causing positive inotropic and chronotropic effects even at therapeutic doses. Acute theophylline poisoning has been linked to myocardial ischemia and myocardial infarction (Hoffman, 2019).

Theophylline and its derivatives have been associated with myocardial infarction in patients without coronary artery disease, leading to elevated troponin levels (Cashy et al., 2020). No prior studies have identified early predictors of cardiovascular toxicity in patients using methylxanthines (Sharif et al., 2023).

This was aligned with Abdelwahab and Hussien, (2020) study which stated that Early identification of theophylline toxicity severity is critical and requires aggressive supportive care to improve patient outcomes.

In this study, the 34 patients were classified into three distinct groups based on their serum theophylline levels (therapeutic range 10–20 mg/L), as outlined by Murray et al., (2011).

This was in accordance with Kuwahara (2022) who stated in his study that, in acute theophylline poisoning, serum theophylline concentration correlates with the severity of the resulting clinical signs. It goes hand in hand with Amin et al., (2013), who found a highly significant relation between theophylline serum level and severity grades of the studied cases according to PSS. They found that the patients with the "none" grade of severity score had a therapeutic serum level (10–20) mg/L, and all minor cases had minimal toxicity serum theophylline level.

In the present study, the age of the patients ranged from 18 to 76 years, and the mean age of theophylline-intoxicated cases was 25.44 ± 11.8. This was explained by (Hodeib and Ghonem, 2019) who revealed that the rate of suicide increases among young adults due to the inability to face life challenges, depression, and anger.

In this study, there is no significant difference between the mild, moderate, and severe groups regarding age, it goes hand in hand with Sharif et al., (2023) study which mentioned that there are no significant variations between studied groups in terms of age. However, it contradicts the study of Shannon and Lovejoy, (1990) who mentioned that age is directly proportional to the frequency of theophylline-associated life-threatening events (LTEs).

In the study, females represented most cases (82.4%). The predominance of females over males in theophylline toxicity was also reported by Oxley-Oxland et al. (2022). Such predominance may be attributed to the relatively high incidence of attempted suicide among females by self-poisoning.

Moreover, the current study revealed that regarding sex, there are no significant differences were observed among the mild, moderate, and severe groups. This is consistent with Sherif et al. (2020), who mentioned that no statistically significant differences were detected among the studied groups regarding sex.

In this study, committing suicide was the main manner of poisoning among the studied cases. Abuelfadl et al. (2017) and Hafez (2018) They also reported that all acute theophylline toxicity cases resulted from suicidal attempts, with no accidental exposures documented in their study.

The study also revealed that 62.5% of severe cases were intoxicated by sustained-release preparations, while 37.5% were by conventional theophylline preparations, and in mild cases, sustained release equal conventional. Hodeib and Ghonem (2019) reported that 63.33% of acute theophylline-intoxicated patients were due to sustained-release preparations. This is supported by the fact that theophylline is commonly available in sustained-release formulations.

Moreover, acute theophylline toxicity was more common than acute on top of therapeutic toxicity among patient groups. However, there was no significant difference between the type of toxicity and severity groups. This was in agreement with Sharif et al., (2023) who mentioned that acute exposure constituted the majority of presented patients with no significant variations between the groups ($P > 0.05$).

In this study, almost all patients showed tachypnea. Abdelwahab and Hussien, (2020), reported similar findings, attributing tachypnea to theophylline's stimulation of central respiratory drive, leading to deep and rapid breathing. This effect involves adenosine receptor antagonism and increased hormone release, including norepinephrine. No significant correlation was found between respiratory rate and severity.

Cardiovascular manifestations were assessed in this study, nearly all patients were tachycardiac, and there were significant differences in pulse rate among the severity groups. These results align with the findings of the study by Naguib et al., (2013), which similarly identified significant differences in pulse rate among mild, moderate, and severe cases.

Most patients were normotensive, while only 8.8% of patients were hypertensive and 5.9% were hypotensive and there is no significant difference between blood pressure and severity groups. These results are in agreement with Delhi et al., (2005), who mentioned that normal blood pressure is a common finding in acute theophylline toxicity cases.

The hypotension in theophylline resulted from severe protracted vomiting, β2 stimulated peripheral vasodilatation and inhibition of PDE with increased

cAMP causing vascular smooth muscle relaxation. In addition, theophylline stimulates β1 receptors in myocytes producing a positive chronotropic effect, which causes a decrease in time for diastolic filling aggravating the hypotensive state (Sherif et al., 2020).

Although, in this study there is no significant difference between mild moderate and severe group in terms of palpitation, shock and cardiac arrest. However, Sharif et al., (2023) study suggests that palpitations could significantly predict life-threatening events (LTEs) which contrasts with Amin et al. (2013) study who found no significant difference between palpitation and severity.

GIT manifestation which reported in the study, most of patients experienced nausea and vomiting. About 62.5% of severe cases had epigastric pain, and half of them had hematemesis. Abdelwahab and Hussien (2020) study supported these results as they found that the most frequent symptoms in theophylline-poisoned patients were nausea and vomiting, followed by abdominal pain. Hematemesis occurred in 8.6% of the cases

Regarding CNS manifestations, irritability represented 70.6% of all cases and 100% of severe cases. Concerning agitation, it represented 100% and convulsions 25% of severe cases, there is a significant difference between mild, moderate, and severe groups. This go hand in hand with Sharif et al., (2023) study who stated that tremors, and irritability were the main symptoms predicting LTEs ($P < 0.05$)

In this study potassium levels also showed that hypokalemia was present in 58.8% of mild cases, 41.7% of moderate cases, and 71.4% of severe cases. With a significant difference between the three studied groups and potassium serum level, potassium levels tend to decrease.

Moreover, the random blood glucose findings indicated hyperglycemia in 61.8% of mild cases, 25% of moderate cases, and 71.4% of severe cases, and there is a statistically significant difference among the three groups.

Abdelwahab and Hussien (2020) explained that hypokalemia in acute theophylline toxicity may result from transcellular shift or gastrointestinal loss, while hyperglycemia is due to increased catecholamine activity. While Cevik et al. (2010) explained that hypokalemia observed in theophylline toxicity is dependent on enzyme inhibition. Also, insulin and glucose increased with theophylline effect, making contributions to the development of hypokalemia.

In Naguib et al. (2013) study, there was a significant difference between mild, moderate, and severe cases regarding serum potassium and random blood glucose levels, they also considered the presence of hypokalemia as a prognostic factor of both single and acute on chronic theophylline overdose, while hyperglycemia was a prognostic factor of single theophylline overdose. Also, Sim et al. (2021) reported that metabolic derangements are more severe in acute theophylline toxicity, and the ones commonly seen include hypokalemia and hyperglycemia.

In the current study, compensated respiratory alkalosis was the most common acid base disorder in all groups, while metabolic acidosis was more prevalent in severe groups, revealing severity. These findings were in agreement with the findings of Hafez (2018) study, which revealed that the highest frequent ABG disturbance was respiratory alkalosis (2.9%), followed by metabolic acidosis (2.5%).

Greene et al. (2018) study attributed that metabolic acidosis in acute theophylline toxicity is commonly attributed to lactic acid, which may be elevated from tissue hypoperfusion or result from muscular hyperactivity, while respiratory acidosis may be seen in patients with central nervous system depression, and respiratory alkalosis is common in awake patients.

In this current study, the mean hospital stay duration is significantly different between groups. The severe group, which represents 23.5 % of patients, shows 2–20 days in the hospital, which is higher than that of the moderate group (41.2%) and mild group (35.3%), as they showed 1–3 and 1–1.5 days, respectively. There are statistically significant differences exist in the durations of hospital stays among the severity groups, with longer stays associated with higher severity.

In addition, there is a statistically significant positive correlation between hospital stay and both CKMB as well as Troponin I level at 6 and 12 hours, suggesting that as hospital stay increases, they tend to increase.

This goes hand in hand with Hafez (2018) study, which revealed that there was an extreme significant difference between the two groups (complicated and non-complicated) regarding the duration of stay.

In this study, 11 patients were admitted to the ICU, while 23 patients were admitted to inpatient care. However, 33 cases survived, and only one case died. There is a significant difference between ICU admission and severity, as well as CKMB and troponin I levels at 6- and 12-hours post ingestion.

Hocaoğlu et al. (2014) study verified that cases with severe acute theophylline toxicity that admitted to ICU need a longer duration for hospital stay as they need close observation and medical care for the proper treatment of complications. Oxley-Oxland et al. (2022) mentioned that severe theophylline toxicity is a common presentation of drug toxicity, requiring admission to the intensive care unit (ICU).

The total number of patients who needed hemodialysis was 7 patients, while 27 patients did not need it. Hemodialysis was significantly high in the severe group 87.5%.

A significant difference was found in hemodialysis rates among the three studied groups, as well as in CK-MB and troponin I levels at 6 and 12 hours post ingestion. Moreover, in troponin I and CKMB, the decreasing p-values from 6 to 12 hours post-ingestion in hemodialysis and ICU admission indicate an increasing significance and suggest that troponin I and CKMB levels become more specific over time in distinguishing patients in need of

hemodialysis, as well as distinguishing between patients admitted to the ICU and those who were not.

Abdelwahab and Hussien (2020) developed a scoring system to predict the need for hemodialysis in acute theophylline poisoning based on clinical and laboratory data. The score includes nine parameters: theophylline level >56.7 mg/l, hospital stay >2 days, pulse >110 beats/min, respiratory rate >27 breaths/min, HCO3 <23 mmol, hematemesis, seizures, agitation, and abnormal ECG. Patients with a TPH score ≥5 had a higher likelihood of requiring hemodialysis.

Concerning CK-MB levels at 6- and 12-hours post ingestion, there is statistically significant variation in CK-MB levels among the three groups (mild, moderate, and severe). The decreasing p-values from 6 to 12 hours post-ingestion suggests that increasing significance in CK-MB levels among severity groups.

After performing post-hoc analyses specifically designed for pairwise group comparisons. At 6 hours post ingestion, there was a significant difference in CK-MB levels between patients with mild and severe toxicity while no significant difference was found between the mild and moderate groups or between the moderate and severe groups. Conversely, at 12 hours post ingestion, a significant difference was observed between mild and severe, mild and moderate groups, but not between the moderate and severe groups.

In the analysis of troponin I levels at both 6- and 12- hours post ingestion, there are significant differences indicating a gradient of severity among the mild, moderate, and severe groups. The highly significant p-value at 12 hours (P = 0.000) suggests a strong difference in troponin I levels among the studied groups.

The post-hoc analyses show significant differences in troponin I levels. At 6 hours post ingestion, the most significant differences are between the mild and moderate groups, as well as between the mild and severe groups. Additionally, at 12 hours post ingestion, there are significant differences in troponin I levels among individuals with mild, moderate, and severe group.

In this study, there is a significant difference between troponin 6, 12 hours, and CKMB 12 hours with the control group. The observed differences suggest that they can effectively differentiate between individuals without toxicity and intoxicated patient. This indicates their potential utility as markers for distinguishing between normal and intoxicated patient.

The absence of a significant difference in CKMB levels at 6 hours post-ingestion between the patient and control groups indicates that CKMB levels at 6 hours post-ingestion cannot effectively distinguish between individuals with the toxicity and those without it. In other words, CKMB lacks the ability to serve as a reliable marker for differentiation between individuals without toxicity and intoxicated patient.

However, a significant association of CKMB was observed with ICU admission and hemodialysis. The diminishing p-values observed from 6 to 12 hours post-ingestion in individuals undergoing hemodialysis and those admitted to the ICU suggest an increasing in significance over time.

This indicates that CKMB can demonstrate heightened sensitivity in detecting severe cases of acute theophylline toxicity, particularly in delayed manifestations as time progresses.

According to Collinson et al. (1992), diagnostic sensitivity of CK-MB is 100% and specificity 100% at Eight hours post-admission, Starakis et al. (2003) reported the elevation of serum CK-MB levels on the second day of hospitalization. So, beyond the 6-hour mark, the accuracy of detecting diseased patients with CKMB significantly improves. However, within the initial 6 hours, CKMB may not reliably serve as a suitable predictor.

Cardiac Troponin I is released in the circulation 6-8 hours after myocardial injury, with peak level at 12-24 hours and remain elevated for 7-10 days (Danese and Montagnana, 2016).

In the current study, Receiver Operating Characteristic (ROC) curve was done to analyze the sensitivity and the specificity of cardiac biomarkers in predicting the severity of acute theophylline toxicity.

Troponin I level measured 6 hours after ingestion had a cut-off value > 0.03, demonstrating a sensitivity of (67.65%) and a specificity of (100%). This suggests that troponin I level measured 6 hours after ingestion is highly specific in identifying severe cases. The notable sensitivity indicates the test's ability to detect a substantial proportion of actual severe cases. The ROC analysis highlights the potential utility of troponin I at 6 hours post-ingestion as a strong predictor for identifying severe cases of acute theophylline toxicity.

Troponin I at 12 hours post ingestion with a cut-off value > 0.03 demonstrates high sensitivity (85.29%) and high specificity (100%). This indicates its effectiveness in accurately identifying individuals with severe cases while correctly excluding those without. While CKMB at 12 hours has a cut-off value ≤ 10.1 shows moderate sensitivity (61.76%) and high specificity (94.12%). It is reasonably good at identifying true positive cases but may have a higher rate of false negatives compared to Troponin I.

So, both Troponin I and CKMB at 12 hours post-ingestion shows promise as diagnostic markers for severe cases. Troponin I, with its higher sensitivity and perfect specificity, appears particularly strong in accurately identifying individuals with severe cases of acute theophylline toxicity.

In summary troponin I level at 6 hours is a strong predictor for identifying severe cases with early manifestations that need ICU admission and hemodialysis, while a troponin I level at 12 hours and a CKMB level at 12 hours post-ingestion appears to exhibit efficacy as promising predictors for severe cases with delayed manifestations. However, troponin I appears to be a stronger indicator for identifying severe cases, striking a balance between sensitivity and specificity, while CKMB, while specific, may not be as sensitive in capturing all cases of severe theophylline toxicity.

This was in agreement with Hodeib and Ghonem (2019) study, which showed that troponin I can predict severity and ICU admission needs in acute theophylline toxicity regardless of presentation time. CK-MB may serve as a predictor in patients with delayed presentation.

Conclusion

1. Troponin I could predict the severity and the requirement of ICU admission and hemodialysis in patients with acute theophylline toxicity either with early or delayed presentation.
2. CK-MB could be considered for patients with delayed presentation.
3. Depending on time of admission, proper choosing of the biomarker to be investigated will allow for better evaluation of patients with saving extra cost.

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العلاقة بين مستوى الثيوفيللين والتروبونين اي مقابل الكرياتين كيناز ام- بي كمؤشرات للتنبؤ بشدة ونتائج التسمم الحاد بالثيوفيللين في البالغين

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الملخص العربي

المقدمة: الثيوفيللين هو أحد مشتقات الميثيل زانثين، ولا يزال يُستخدم على نطاق واسع في العديد من الدول النامية لعلاج الربو الشعبي الحاد والمزمن. وتستمر شعبيته نظرًا لفعاليته، تكلفته المنخفضة، وتوفره الواسع. مع ذلك، فإن حالات التسمم الحاد بالثيوفيللين تشكل خطرًا كبيرًا لعدم وجود مضاد للتسمم خاص له. هناك حاجة كبيرة للتنبؤ بشدة ونتائج حالات التسمم الحاد بالثيوفيللين من أجل اتخاذ القرار العلاجي المناسب.

طريقة البحث: الهذه الدراسة هي دراسة جماعية استباقية أُجريت على ٣٤ مريضًا تم إدخالهم إلى مركز السموم بمستشفيات جامعة عين شمس خلال فترة ٦ أشهر من يناير ٢٠٢٢ إلى يونيو ٢٠٢٢، وكان لديهم تاريخ تعرض حاد لتسمم بالثيوفيللين. تم قياس مستويات كل من التروبونين اي وإنزيم الكرياتين كيناز ام- بي بعد ٦ ساعات و١٢ ساعة من دخول المستشفى.

النتائج: أظهرت النتائج أن مستويات التروبونين اي بعد ٦ ساعات و١٢ ساعة من التسمم، وكذلك مستوى إنزيم الكرياتين كيناز ام- بي بعد ١٢ ساعة، كانت مرتفعة بشكل ملحوظ في المرضى الذين تعرضوا لتسمم حاد شديد بالثيوفيللين، وفي المرضى الذين احتاجوا إلى دخول وحدة العناية المركزة أو الخضوع للغسيل الكلوي.

الاستنتاج: يمكن استخدام التروبونين أي كمؤشر للتنبؤ بشدة التسمم والحاجة إلى دخول العناية المركزة أو إجراء الغسيل الكلوي في حالات التسمم الحاد بالثيوفيللين، سواء كانت الحضور مبكرًا أو متأخرًا، بينما يمكن الاستفادة من إنزيم الكرياتين كيناز ام – بي في تقييم المرضى الذين يصلون في وقت متأخر بعد التسمم.

التوصية: يُوصى باستخدام التروبونين كمؤشر للتنبؤ بشدة الحالة في المرضى المصابين بالتسمم الحاد سواء في الحالات ذات العرض المبكر أو المتأخر. ويُفضل استخدام إنزيم الكرياتين كيناز ام – بي كمؤشر للتنبؤ بشدة الحالة في المرضى المصابين بالتسمم الحاد في حالات العرض المتأخر فقط.

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