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Research Paper

Rhabdomyolysis and High-sensitivity Troponin I Activity in Acutely Intoxicated Patients

Aleksandra Babulovska[1*], Lidija Petkovska[1], Zanina Pereska[1], Natasha Simonovska[1], Afrodita Berat-Huseini[1], Kristin Kostadinoski[1], Kiril Naumoski[1]

[1] *University Clinic for Toxicology, 1000 Skopje, Republic of North Macedonia, Faculty of Medicine, Ss. Cyril and Methodius, University in Skopje, 1000 Skopje, Republic of North Macedonia*

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*** Corresponding author:**
Aleksandra Babulovska, University Clinic for Toxicology, 1000 Skopje, Republic of North Macedonia, Faculty of Medicine, Ss. Cyril and Methodius, University in Skopje, 1000 Skopje, Republic of North Macedonia

E- mail: ababulovska@yahoo.com

ABSTRACT

Background: This study evaluated the high-sensitivity Troponin I (hs-TnI) activity in patients with rhabdomyolysis following acute intoxication with either psychotropic drugs or other chemical agents.
Methods: This study randomly recruited 140 patients suffering from rhabdomyolysis. They were divided into two groups affected by either psychotropic drugs or chemical agents. hs-TnI was measured in all patients with rhabdomyolysis three times (i.e., the first, third, and fifth days of hospitalization).
Results: The mean hs-TnI values on the first, third, and fifth days were obtained at 27.7±78.3 µg/L, 43.7±135.9 µg/L, and 28.73±57.01g/L, respectively. On the third day of hospitalization, hs-TnI was significantly higher in all patients, compared to the fifth day. According to the intoxication agent on the first day, the highest values of hs-TnI were determined in methadone intoxications (N = 5) - 279.7 ± 190.7 µg / L, benzodiazepines (N = 3) - 213.9 ± 232.5 µg / L, other drugs (N = 1) - 138.4 µg / L. Analysis by the type of intoxication on the first, third, and fifth days showed that hs-TnI values were insignificantly higher in the psychotropic group, compared to the chemical group.
Conclusion: Clinicians should be aware of the possibility of increasing hs-TnI in patients with rhabdomyolysis due to acute intoxication. Elevated levels of hs-TnI in psychotropic intoxications were likely related to the specific etiologies, such as illicit substance use, while chemical intoxication was associated with the clinical outcome of intoxication.

Keywords: Creatine kinase, Illicit drugs, Toxicity

Introduction

Rhabdomyolysis is a pathological condition in which skeletal muscle necrosis occurs, resulting in the leakage of intracellular muscle contents, such as myoglobin and creatinine kinase, into the circulation. Common causes include crush injuries, heat injuries, toxins, and overexertion [1]. Mechanisms by which toxicants cause rhabdomyolysis are variable and include prolonged unconsciousness and immobility, agitation, seizures, fall, withdrawal and hyperthermia [1]. The classic presentation of this condition includes muscle pain, muscle weakness, and dark-colored urine [2]. This is the classic triad of symptoms; however, it occurs in only about 10% of patients, while up to 50% of patients present no clinical symptoms [3].

Cardiac troponins are regulatory proteins of the thin filament of striated muscle and consist of three tightly interconnected subunits: T (cTnT, 37 kDa), I (cTnI, 24 kDa), and C (cTnC, 18 kDa). A troponin complex together with tropomyosin is located on the actin filament and is essential for the regulation of calcium-mediated contraction of skeletal and cardiac muscles [4]. Although release of cTn indicates myocardial injury, the finding is not pathognomonic of acute coronary syndrome (ACS). Elevated serum cTn values may result from myocardial damage due to inflammation, intoxication, malignancy, or degeneration. Elevated troponin values can be found in a variety of diseases unrelated to ACS [5]. Cardiac troponins may occasionally be elevated in patients with rhabdomyolysis [6,7].

Our ability to accurately measure cardiac troponin has improved through the development of more sensitive assays, with the latest generation of high-sensitivity assays capable of detecting cardiac troponin concentrations in majority of healthy individuals. This has allowed accurate identification of the normal

reference range and the 99th centile upper reference limit [8].

Aim of the study: Given the absence of published literature similar to the present study, we planned to compare and contrast the hs-Troponin I activity in patients with rhabdomyolysis secondary to acute intoxication with either psychotropic or chemical substances.

Materials and Methods

This clinical trial was conducted in a one-year period at the University Clinic for Toxicology, Republic of North Macedonia. As a prospective study, 140 patients with rhabdomyolysis were recruited and divided into two groups based on the toxic substance they consumed.

Patients' Grouping and Inclusion Criteria: Patients were divided into two groups based on the following inclusion criteria:

- ***Group 1*:** Patients poisoned with psychotropic agents, e.g., heroin and methadone.
- ***Group 2*:** Patients intoxicated with other chemical agents.

Rhabdomyolysis was defined as a creatinine kinase (CK)>250 U/L according to the poisoning severity score (PSS). We included adult patients aged 18 years and older with rhabdomyolysis. They had been acutely intoxicated with either psychotropic or chemical substances within the 48 h prior to admission into the hospital.

Exclusion Criteria: We excluded patients with myocardial infarction, renal impairment, acute and chronic hepatitis B and C, and other hepatic impairments based on their medical history. Informed consent from the patients was obtained prior to their inclusion in the study. The study was approved by the Ethics Commission of the Faculty of Medicine, Republic of North Macedonia.

Statistical analysis: The collected data was analyzed with the help of the SPSS statistical software (version 22). The quantitative data were analyzed in series, using central tendency (mean and median) and dispersion measures (standard deviation and IQR). Mann-Whitney U test was used to compare the average values based on data distribution. Spearman's correlation coefficients were used to determine the relationship among numerical variables. A *P*-value less than 0.05 was considered statistically significant.

Results

A total of 1,446 patients diagnosed with acute intoxications were treated during the study period at the University Clinic for Toxicology in Skopje, Republic of North Macedonia. Of this total, 140 patients developed rhabdomyolysis. Ninety-six (68.6%) of the patients with rhabdomyolysis had been poisoned with psychotropic drugs (*Group 1*), while the remaining 44 (31.4%) individuals had consumed chemical agents (*Group 2*). Intoxications with psychotropic substances were significantly more frequently observed than those with chemical substances.

On average, male patients were about four years younger than female ones (40.8 vs. 44.1); however, the age difference between the two groups was statistically insignificant based on Mann-Whitney test.

High-sensitivity troponin (hs-TnI) was measured in all patients with rhabdomyolysis three times, during the first, third, and fifth days of hospitalization. Testing the distribution for hs-cTnI three times showed the existence of an irregular distribution for the consequently Shapiro-Wilk W=0.3691; P=0.000001 vs. Shapiro-Wilk W=0.3047; P=0.000001 vs. Shapiro-Wilk W=0.5338; P=0.000001.

Day 1 No significant difference was observed between the two groups of patients regarding the level of hs-cTnI on the first day (Mann-Whitney U Test: Z=-0.7625; P=0.4457; Table 1).

Table 1. Analysis of patients with rhabdomyolysis according to the type of intoxication and hs-cTnI levels at three time points

hs-cTroponin I		(N)	(Mean)	(Std. Dev.)	(Min)	(Max)	Percentiles		
							25th	50th (Median)	75th
Day 1	Psychotropic	92	31.45	91.22	0.31	515.00	1.45	3.50	7.90
	Chemical	40	19.07	32.80	0.60	138.42	2.18	4.35	15.02
	Total	132	27.70	78.31	0.31	515.00	1.50	4.10	8.20
				Mann-Whitney U Test: Z=-0.7625; P=0.4457					
Day 3	Psychotropic	35	25.74	57.75	1.00	328.00	2.10	6.20	36.00
	Chemical	20	75.24	211.95	1.00	958.20	3.50	15.60	40.00
	Total	55	43.74	135.95	1.00	958.20	2.80	7.10	39.00
				Mann-Whitney U Test: Z=-1.1285; P=0.2591					
Day 5	Psychotropic	12	17.46	31.45	1.10	112.00	2.60	5.85	13.84
	Chemical	11	41.01	75.79	0.34	259.43	1.30	4.00	52.00
	Total	23	28.73	57.01	0.34	259.43	2.10	5.50	35.63

Mann-Whitney U Test: Z=0.1539; p=0.8777
1/3/5 - Friedman Test: N=20 Chi-Square=15.101; df=2; P=0.001*
3/5 - Wilcoxon Signed Ranks Test: Z=-3.55; P=0.0001*
3/1- Wilcoxon Signed Ranks Test: Z=-1.903; P=0.057
5/1 - Wilcoxon Signed Ranks Test: Z=-2.315; P=0.021
*Significantly for P<0.05
hs-cTnI reference values: women ≤ 15.6 µg/L; men ≤34.2 µg/L

The highest hs-cTnI levels in Group 1 were as follows:

a) Methadone (N=5) – 279.7 ± 190.7 µg/L, with min./max. 73.4/515 µg/L, and in 50% of patients with a value above Median=311 µg/L;

b) Benzodiazepines (N=3) – 213.9 ± 232.5 µg/L, with min./max. 37/477.3 µg/L, and in 50% of patients

with a value above Median=127 µg/L.

The highest hs-cTnI levels in Group 2 were:

a) Other drugs (N=1) – 138.4 µg/L.

Analysis by the type of intoxication showed that hs-cTnI levels were non-significantly higher in group 1 (Median=100 µg/L) compared to group 2 (Median=181 µg/L) for a consistent Mann-Whitney U Test: Z=-0.740; P=0.4592.

Day 3 According to the type of intoxication, hs-cTnI levels were non-significantly higher in group 1 (Median=47 µg/L) compared to group 2 (Median=43.5 µg/L; Table 2).

Table 2. Analysis of patients with rhabdomyolysis and elevated hs-cTnI levels according to etiological cause and type of intoxication at three time points

Intoxication		hs-cTnI (µg/L)					
		(N)	(Mean)	(Std. Dev.)	(Min)	(Max)	Median
Etiological cause							
Day 1	benzodiazepine	3	213.90	232.55	37.00	477.30	127.40
	antipsychotic	2	106.70	114.26	25.90	187.49	106.70
	antidepressants	1	32.00	0.00	32.00	32.00	32.00
	herbicides	1	138.42	0.00	138.42	138.42	138.42
	organophosphates	1	81.00	0.00	81.00	81.00	81.00
	corrosives	3	69.68	28.18	46.40	101.00	61.63
	heroin	4	78.48	28.88	58.00	121.30	67.31
	methadone	5	279.70	190.70	73.40	515.00	311.00
	ethylen glycol	1	94.52	0.00	94.52	94.52	94.52
	CO	1	54.00	0.00	54.00	54.00	54.00
Type of intoxication							
Day 1	Psychotropic	15	173.30	168.08	25.90	515.00	100.0
	Chemical	7	82.42	32.06	46.60	138.42	81.00
	Total	22	144.39	144.93	25.90	515.00	87.76
Mann-Whitney U Test: Z=-0,740; P=0,4592							
Day 3	Psychotropic	9	84.56	94.15	36.00	328.00	47.00
	Chemical	8	177.16	319.48	36.00	958.20	43.55
	Total	17	128.13	226.62	36.00	958.20	46.10
Mann-Whitney U Test: Z=-0,386; P=0,7011							
Day 5	Psychotropic	2	75.00	52.32	38.00	112.00	75.00
	Chemical	5	88.14	96.27	35.63	259.43	52.00
	Total	7	84.38	81.70	35.63	259.43	52.00
Mann-Whitney U Test: Z=-0,391; P=0,6961							

*Significantly for P<0.05

Day 5 According to the type of intoxication, hs-cTnI levels were insignificantly higher in group 1 (Median=75 µg/L) than in group 2 (Median=52 µg/L; Table 2).

We found that:

a) Group 1 patients with elevated hs-cTnI levels had a significantly higher creatinine phosphokinase (CPK) and CK-MB level compared to those with normal hs-cTnI levels;

b) Group 2 - There was no significant difference in CPK level between patients with normal or elevated hs-cTnI levels. Patients with elevated hs-TnI levels had a significantly higher CK-MB level compared to those with normal hs-cTnI levels (Table 3).

Table 3. Correlation of hs-TnI with CPK and CK-MB on the first day according to the type of intoxication

Parameters		(N)	(Mean)	(Std. Dev.)	Percentiles			*P-value*
					25th	50th (Median)	75th	
CPK - Psychotropic								
hs –TnI	Normal	81	4476.2	13092.0	451.2	753.0	1827.7	Mann-Whitney U Test:
	Elevated	15	21896.6	32843.3	1492.0	10776.0	25834.4	Z=-3.1987; P=0.0013*
CPK – Chemical								
hs –TnI	Normal	37	2639.3	8538.4	339.6	474.0	1025.8	Mann-Whitney U Test:
	Elevated	7	1649.4	2012.5	421.0	589.0	3350.0	Z=-0.8182; P=0.4132
CK-MB - Psychotropic								
hs –TnI	Normal	81	155.6	453.7	22.7	37.0	89.0	Mann-Whitney U Test:
	Elevated	15	430.2	608.0	37.0	186.1	732.9	Z=-3.0221; P=0.0025*
CK-MB - Chemical								
hs –TnI	Normal	37	54.8	83.8	28.0	31.3	46.5	Mann-Whitney U Test:
	Elevated	7	105.1	78.9	33.0	133.4	135.0	Z=-1.9894; P=0.0466*

*Significantly for P<0.05

Influence of high-sensitivity Troponin I on the hospital length of stay in patients acutely intoxicated with rhabdomyolysis.

a) Group 1 - The hs-TnI level on admission significantly affected the length of stay in 17.7% of patients (R2=0.177). Increasing the hs-TnI level per unit on admission increased the length of hospital stay by an average of 0.016 days.

b) Group 2 - The hs-TnI level on admission had no influence on the hospital length of stay (R2=0.000). The increased hs-TnI level on the first day did not affect the hospital length of stay variability.

Discussion

In our study, hs-TnI on the first day was elevated in 15.7% of acutely intoxicated patients with rhabdomyolysis. According to the literature, an elevated serum troponin value occurs in 11-30% of patients with rhabdomyolysis [9,6]. In a study by Benoist *et al.*, 33% of patients had elevated serum cTnI values as a result of posttraumatic rhabdomyolysis [10]. In patients with rhabdomyolysis after surgery, in an analysis made by a group of authors, 35% of the patients showed elevated values of cTnI [11]. In our study, the hs-TnI levels on the third day were significantly higher compared to those on the fifth day, as well as borderline insignificantly higher compared to the first day. Increased serum values of hs-TnI on the first day of hospitalization were detected in 10.7% of patients with rhabdomyolysis acutely intoxicated with psychotropic substances and in 5% of those intoxicated with chemical substances. In the group intoxicated with psychotropic substances, patients who tested positive for hs-TnI included those who overdosed on methadone and heroin, followed by individuals intoxicated with benzodiazepines, primarily those with opioid addiction, as well as antipsychotics and tricyclic antidepressants (TCA). In the group intoxicated with chemical substances, those who tested positive for hs-TnI included individuals intoxicated with corrosive agents, other drugs, carbon monoxide (CO), and herbicide. The hs-TnI level was non-significantly higher in the psychotropic group than in the chemical intoxication group.

Electrocardiogram (ECG) and changes were not verified in patients with increased hs-TnI levels. Thus, relying solely on troponin levels, in the presence of a normal ECG, to diagnose myocardial ischemia can lead to unnecessary and expensive invasive testing. Therefore, it is important for clinicians to keep in mind the various causes of troponin elevations in order to provide the highest value care to patients. In patients with rhabdomyolysis who are acutely intoxicated with psychotropic intoxications, as the level of hs-TnI increased, the level of CPK also increased significantly. In the group with chemical intoxications, as hs-TnI levels increased, the level of CPK increased insignificantly. In patients intoxicated with psychotropic substances and experiencing rhabdomyolysis, as hs-TnI levels increased, the level of CK-MB also increased significantly. In the group intoxicated with chemical substances, we observed that as hs-TnI levels increased, the level of CK-MB increased insignificantly. In the psychotropic group, there was a relationship between the severity of rhabdomyolysis and the degree of serum hs-TnI elevation. In the study by Punukollu *et al.*, no correlation between peak serum CK activity and serum cTnI levels was found [9]. There was no relationship between the severity of rhabdomyolysis and the degree of serum cTnI elevation [9]. Data on the differences between "classic" troponins and high-sensitivity troponins in this clinical context are lacking. In the chemical group, potential injury to the myocardium should be determined in those intoxicated with CO [12]. Patients from the chemical group with elevated hs-TnI were classified into mild and moderate groups according to the PSS. Troponin I elevation in critical illness is common and multifactorial. Positive cTnI in this cohort likely represent an epiphenomenon of multiple organ failure (MOF) [13].

Limitations

This study included only individuals who were acutely intoxicated with rhabdomyolysis at our clinic; therefore, the generalizability of the results may be limited. Another limitation of the study is that we do not have the results of the indicated echocardiography because the patients were discharged from the hospital, and patients were not followed after discharge.

Conclusions

Clinicians should be aware of the possibility of increasing high-sensitivity troponin I in patients with rhabdomyolysis due to acute intoxication, and therefore, further invasive investigations may be unnecessary. In cases of psychotropic intoxication, the increased level of hs-TnI was associated with specific etiologies such as the use of illicit substances. In contrast, chemical intoxication was associated with the clinical outcomes of the intoxication.

Conflict of Interests

None.

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Compliance with Ethical Guidelines

This study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius, University in Skopje, 1000 Skopje, Republic of North Macedonia (Ethics Code: 03-1864/4; dated 19.04.2019).

Authors' Contributions

Aleksandra Babulovska: a. conception; b.study design, methods used;e.writing the manuscript;

Lidija Petkovska: c. acquisition and collation of data;

Zanina Pereska: d. analysis, interpretation of data;

Natasha Simonovska: e. writing the manuscript;

Afrodita Berat Huseini: f. critical revision of paper;
Kristin Kostadinoski: b.study design, methods used;
Kiril Naumoski: other. performed patients' clinical management

All authors revised and approved the final version of the manuscript.

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