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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Acute kidney injury and necessity of renal replacement therapy in acutely intoxicated patients with rhabdomyolysis

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SUMMARY

Introduction/Objective This study aimed to analyse the characteristics of the selective parameters related to the development of acute kidney injury and the necessity of renal replacement therapy in patients with rhabdomyolysis due to acute intoxication with psychotropic and chemical substances in the first 24 hours.

Methods In a clinically controlled prospective study, 140 patients with rhabdomyolysis were divided into two groups depending on the intoxicating substance, i.e., psychotropic or chemical. Patients were selected according to predetermined inclusion and exclusion criteria.

Results Acute kidney injury occurred in 15% of 140 patients with rhabdomyolysis of whom 14 (66.7%) had psychotropic intoxication and seven (33.3%) had chemical intoxication. Statistical analysis showed significantly increased prevalence in the psychotropic group compared to those with chemical intoxication (p 0.0002). Creatine kinase values for median interquartile range in patients without/with renal replacement therapy were in psychotropic – 753 (446–753) *vs*. 42,670 (22,357–42,670) U/L; and chemical – 478.3 (321.5–1111.9) *vs*. 648.6 (495.6–2065) U/L. In psychotropic intoxications this difference was significant (p = 0.00002), while in the chemical ones it was insignificant (p = 0.2885). The renal replacement therapy was applied in 13 (9.3%) patients with rhabdomyolysis, nine of which (69.2%) were with psychotropic intoxication and four (30.8%) were with chemical intoxication.

Conclusion The prevalence of acute kidney injury and necessity for necessity for renal replacement therapy was significantly higher in psychotropic intoxication compared to chemical intoxication. The level of creatine kinase and myoglobin on the first day in the group with psychotropic substances, and high-sensitivity troponin I in both groups –psychotropic and chemical substances – are significantly higher in patients who need renal replacement therapy compared to those who do not need this therapy.

Keywords: toxicity; creatine kinase; myoglobin

INTRODUCTION

Rhabdomyolysis (RML) is a clinical syndrome resulting from the destruction of muscle fibers and the consequent release of intracellular constituents, such as myoglobin, creatine kinase (CK), and lactate dehydrogenase (LDH) into the bloodstream, which have the potential to cause local and systemic complications [1]. Common causes include crush injuries, heat injuries, toxins, and overexertion [2].

The most common life-threatening complication of RML is acute kidney injury (AKI). Some possible causes are direct tubular toxicity of myoglobin, vasoconstriction, formation of intra-tubular casts, and renal ischemia caused by low blood volume [3]. Myoglobin released from damaged muscles is a major renal injury factor deposited in renal tubules [4]. During muscle breakdown, excessive amounts of myoglobin are released, exceeding the renal threshold, leading to myoglobinuria and renal damage [4]. As an iron-containing protein, it has the ability to bind molecular oxygen, which may produce a hydroxyl radical in the oxidation of ferrous oxide (Fe_2+) to ferric oxide (Fe_3+) [5]. Nephrotoxic effects of myoglobin through free radical production and lipid peroxidation leading to renal vasoconstriction and oxidative damage to renal tubules also contribute to the development of AKI [6]. Metabolic acidosis and increased uric acid concentrations potentiate the nephrotoxic properties of myoglobin through its precipitation and interaction with Tamm-Horsfall protein to form casts in tubules [7]. Patients with AKI are classified into three clinical stages based on increase in creatinine and/or decrease in urine output, according to Kidney Disease Improving Global Outcomes (KDIGO) recommendations [8].

This study aimed to analyze the characteristics of the selective parameters related to the development of AKI and the necessity of renal replacement therapy in patients with RML due to acute intoxication with psychotropic and chemical substances in the first 24 hours.

METHODS

This was a prospective clinical study conducted during 2019 at the University Clinic for

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Toxicology in Skopje. The study included patients with RML divided into two groups, depending on the toxic substance consumed by them (psychotropic or chemical). RML was defined as a creatinine kinase (CK) > 250 U/L according to the Poisoning Severity Score. We included adult patients aged 18 years and older with RML. They had been acutely intoxicated with either psychotropic or chemical substances within the 48 hours prior to admission to the hospital. We excluded patients with pre-existing renal disease, chronic renal disease, muscle trauma as a result of a traumatic accident and patients with myocardial infarction. According to KDIGO criteria, the AKI was categorized as AKI I, II, or III based on the increase in serum creatinine ≥ 26.5 μmol/L or an increase to ≥ 1.5-fold to two-fold from baseline, > twofold to threefold from baseline, and > threefold from baseline or serum creatinine ≥ 354 μmol/L [8]. Individuals who receive renal replacement therapy were considered to have met the criteria of AKI III regardless of their serum creatinine value.

Patients' informed consent was obtained prior to their inclusion in the study.

The study was approved by the Ethics Commission of the Faculty of Medicine, Ss. Cyril and Methodius at the University of Skopje, Republic of Northern Macedonia (Ethics Code: 03-1864/4; dated 19.04.2019).

Statistical analysis

The data obtained in the study were analyzed using IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA). The quantitative data were analyzed in series, using central tendency (mean and median) and dispersion measures (standard deviation and interquartile range – IQR). Fisher's exact test was used to determine the association among certain features in the group of subjects. Mann–Whitney U test was used to compare the average values, according to distribution. Values of $p < 0.05$ were considered statistically significant. The binary logistic regression was used to identify the predicative parameters for developing AKI.

RESULTS

A total of 1446 patients diagnosed with acute intoxications received treatment during the study period at the University Clinic for Toxicology in Skopje, Republic of North Macedonia. Among them, 140 patients developed RML. Ninety-six (68.6%) patients with RML were poisoned with psychotropic drugs, while the remaining 44 individuals (31.4%) ingested chemical agents. Intoxications involving psychotropic substances were significantly more common than those involving chemical substances.

Among patients with RML, a total of 21 (15%) had AKI, with 14 (66.7%) resulting from psychotropic intoxication and seven (33.3%) from chemical intoxication. The analysis revealed a significantly higher prevalence of AKI in psychotropic intoxications compared to chemical intoxications (difference 33.4% [(15.6–48.2) 95% CI]; $\chi^2 = 13.552$; df = 1; p = 0.0002).

In the group with psychotropic intoxications and AKI, 13 (92.8%) were male and one (7.14%) was female, while in the group with chemical intoxications, the distribution was three (42.86%) male and 4 (57.1%) female. The average age of patients with RML and AKI in the psychotropic intoxication group was 39.9 ± 13.4, with a range of 26–53 years, compared to 57.8 ± 15.1 years, with a range of 41–82 years in the chemical intoxication group. Median IQR age distribution indicated that 50% of patients in the psychotropic intoxication group were under 40 years old [median IQR = 40 (36–47)], while in the chemical intoxication group, 50% were under 54 years old [median IQR = 54 (52–65)]. There was a significantly older patient population in the group with chemical intoxications (Mann–Whitney U Test: Z = -3.0597; p = 0.002221*) (Table 1).

We individually analyzed the etiological factors for AKI, considering the prevalence of psychotropic and chemical parameters (Table 2). In psychotropic intoxications, AKI occurred in 14 (14.6%) patients, with the highest prevalence found in the following: a) heroin three (60%); b) methadone six (40%); c) neuroleptics three (25%); d) anticonvulsants one (17.7%); and e) antidepressants one (8.3%). In chemical intoxications, AKI was reported in seven (15.9%) patients, with the highest prevalence in ethylene glycol (1; 100%) and herbicides (1; 33.3%), followed by insecticides (3; 20%) and corrosives (2; 16.7%).

With stage I acute renal injury there were two (9.53%) patients, stage II had six (28.57%) patients, and stage III consisted of 13 (61.90%) patients in need of renal replacement therapy. A total of 13 (9.3%) patients with RML received renal replacement therapy, of which nine (69.2%) had psychotropic intoxication and four (30.8%) had chemical intoxication. The analysis showed a significantly higher prevalence of renal replacement therapy (RRT) in psychotropics compared to chemical intoxications (difference 38.4% [(20.7–52.7) 95% CI]; $\chi^2 = 18,036$; df = 1; p = 0.0001). Out of 21 patients diagnosed with AKI, 13 (61.9%) received RRT, while eight (38.1%) did not require this therapy.

In the group of psychotropic intoxications, RRT was applied in 9 (9.4%) patients. The prevalence of RRT according to etiological cause was the highest in the following: a) heroin two (40%); and b) methadone four (26.7%); followed by c) neuroleptics three (25%). In chemical intoxications, RRT was applied in four (9.1%) patients. The prevalence of RRT according to etiological cause was highest in ethylene glycol (1; 100%) and herbicides (1; 33.3%), followed by insecticides (1; 6.7%) and corrosives (1; 8.3%).

We analyzed the association of AKI with selected parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), troponin, and myoglobin obtained on the first day of hospitalization of patients with RML (Table 3).

We found that patients with AKI from the whole sample with RML as well as those in the psychotropic intoxications group had significantly higher values for all selected parameters compared to those without AKI. However, the whole sample with RML had insignificantly higher values for Na (p = 0.89) (Table 3). Regarding the group with

Table 1. Demographic characteristics of the study population

Parameter		Total
Type of intoxication		
Psychotropic	n (%)	14 (66.67)
Chemical	n (%)	7 (33.33)
Difference test: Difference 33.34% df 1; p 0.0001*		
Sex		
Psychotropic	Men n (%)	13 (92.86)
	Women n (%)	1 (7.14)
Chemical	Men n (%)	3 (42.86)
	Women n (%)	4 (57.14)
Pearson's χ^2 test 6.4312 df 1; p 0.011213*		
Age		
Psychotropic	$\bar{X} \pm SD$	39.93 ± 13.41
	Min/Max	26/53
	Median (IQR)	40 (36–47)
Chemical	$\bar{X} \pm SD$	57.86 ± 15.18
	Min/Max	41/82
	Median (IQR)	54 (52–65)
Mann–Whitney U Test: Z -3.0597; p 0.002221*		

*Significant for $p < 0.05$

Table 2. Etiological agent of acute kidney injury (AKI) and renal replacement therapy (RRT) in patients with rhabdomyolysis

Etiological agents		Total	AKI		RRT	
		N	N	%	N	%
1	Benzodiazepines	20	0	0	0	0
2	Neuroleptics	12	3	25	3	25
3	Anticonvulsants	6	1	16.7	0	0
4	Antidepressants	12	1	8.3	0	0
5	Antiparkinsonic	2	0	0	0	0
6	Heroin	5	3	60	2	40
7	Methadon	15	6	40	4	26
8	Amfetamines	4	0	0	0	0
9	Cocain	1	0	0	0	0
10	Tramadol	3	0	0	0	0
11	Ethyl alcohol	15	0	0	0	0
12	Canabis	1	0	0	0	0
13	Other	1	0	0	0	0
14	Calcium-channel inhibitor	2	0	0	0	0
15	Herbicides	3	1	33.3	1	33.3
16	CO	7	0	0	0	0
17	Other gases	1	0	0	0	0
18	Gasoline	2	0	0	0	0
19	Ehylen glycol	1	1	100	1	100
20	Insecticides	15	3	20	1	6.67
21	Corrosive agents	12	2	16.7	1	8.3
	Total	140	21	15	13	9.3

chemical intoxications, we found that patients with AKI had insignificantly higher values for the following parameters: Na ($p = 0.311$), K ($p = 0.22$), Ca ($p = 0.25$), AST ($p = 0.3277$), ALT ($p = 0.9616$), and high-sensitivity troponin I ($p = 0.0051$) compared to those without AKI. For the other parameters, the values observed in patients with AKI in this group were insignificantly higher compared to those without AKI for CK ($p = 0.8348$) and myoglobin ($p = 0.1127$) (Table 3).

In the whole sample as well as individually in the groups with psychotropic or chemical intoxication, we found that the level of CK on the first day was higher in patients with RRT compared to those without this therapy (Table 4). CK values for median IQR in patients without/with RRT were as follows: a) whole sample – 634 (339.6–1532) *vs.* 22,357 (3350–42,670) U/L; b) psychotropic – 753 (446–753) *vs.* 42,670 (22,357–42,670) U/L; and c) chemical – 478.3 (321.5–1111.9) *vs.* 648.6 (495.6–2065) U/L. In the whole sample and in psychotropic intoxications, this difference was significant ($p = 0.00004$ *vs.* $p = 0.00002$), while in the chemical ones it was insignificant ($p = 0.2885$).

The value of myoglobin on the first day in the whole sample as well as individually in the groups with psychotropic or chemical intoxications was higher in patients with RRT compared to those without this therapy (Table 4). Myoglobin values for median IQR in patients without/with RRT were as follows: a) whole sample – 155.3 (126.8–425.2) *vs.* 1018.5 (604.3–3741.5); b) psychotropic – 186.2 (12.7–568.4) *vs.* 1308.5 (1018.5–6421.5); and c) chemical – 140.7 (126.8–291.1) *vs.* 454.5 (227.4–604.3). In the whole sample and in psychotropic intoxications group, this difference was significant ($p = 0.00002$ *vs.* $p = 0.00003$), while in the chemical intoxications group it was insignificant ($p \neg 0.1081$). The value of troponin on the first day in the whole sample as well as individually in the groups with psychotropic or chemical intoxications was higher in patients with RRT compared to those without RRT (Table 4). High-sensitivity troponin I values for median IQR in patients without/with RRT were as follows: a) whole sample – 3.1 (1.3–6.9) *vs.* 83.9 (14.1–111.1); b) psychotropic – 2.3 (1.3–6.8) *vs.* 73.4 (19.9–121.3); and c) chemical – 3.7 (2.2–8.2) *vs.* 94.5 (5.2–101). In all, this difference was significant for the consequent $p = 0.00004$ *vs.* $p = 0.00003$ *vs.* $p = 0.0481$.

The results of Fisher's exact test ($p = 0.018$) indicate a significant association between AKI and the used substance in poisoning (Table 5). The adjusted residuals showed a significantly higher presentation of AKI in poisoning with heroin, methadone in the psychotropic group, and ethylene glycol in the chemical group and significantly lower presentation in poisoning with benzodiazepines in the psychotropic group than expected.

The adjusted residuals were used as a parameter to present the significance of the difference between the AKI+ and AKI- groups for each type of poisoning.

A logistic regression was performed to ascertain the effects of age, sex, group of substances, creatinine, and creatine phosphokinase (CPK) on the likelihood that participants have AKI. The logistic regression model was statistically significant, $\chi^2(5) = 83.389$, $p < 0.0001$ (Table 6). The model explained 78% (Nagelkerke R^2) of the variance in AKI and correctly classified (percentage accuracy in classification) 95.7% of cases, with PPV being 94.2% and NPV 95.9%. Only creatinine was a significant predictor of the likelihood that participants had AKI. The increase in creatinine for one unit was 1.05 times more likely to exhibit AKI with 95% CI 1.016–1.083. Increasing CPK, age, use of psychotropic drugs, and male sex insignificantly increased the likelihood of exhibiting AKI.

Table 3. Acute kidney injury and laboratory parameters according to the type of intoxication

Parametar			N	Average (Mean)	Standard deviation	Percentiles			p
						25th	50th (median)	75th	
BUN	Psychoactive								
	AKI	no	82	4.9	3	3.3	4.5	5.5	Z -5.555;
		yes	14	18.1	10.4	9.9	14.1	25.3	p > 0.001*
	Chemical								
	AKI	no	37	5.9	2.5	4.1	5.4	6.8	Z - 2.087;
		yes	7	10.3	5.9	5.9	7.3	16.1	p 0.037*
	Total								
	AKI	no	119	5.2	2.9	3.5	4.7	5.8	Z -5.906;
		yes	21	15.5	9.7	7	12.6	22.7	p > 0.01*
Creatinine	psychoactive								
	AKI	no	82	81	18.9	65.8	78	91.6	Z -5.949;
		yes	14	332.7	255.4	209.8	277.1	359.3	p > 0.001*
	chemical								
	AKI	no	37	86.9	23.4	73.8	83	105.1	Z -2.070;
		yes	7	170.6	103.7	69	145.8	279	p 0.038*
	Total								
	AKI	no	119	82.8	20.5	67	79	96	Z -6.143;
		yes	21	278.6	227.5	143.4	272.9	333.9	p > 0.01*
Na	Psychoactive								
	AKI	no	82	137.5	4.3	136	138	139.6	Z -2.915;
		yes	14	131.1	7.6	125	131.5	139	p 0.004*
	Chemical								
	AKI	no	37	137.8	3.5	136	137	140.1	z -1.012;
		yes	7	141.6	8.5	134.6	140	144	p 0311
	Total								
	AKI	no	119	137.6	4.1	136	138	139.8	Z -1.699;
		yes	21	134.6	9.2	129	134.6	139.6	p 0.89
K	Psychoactive								
	AKI	no	82	4	0.7	3.6	3.9	4.5	Z - 3.630;
		yes	14	5.4	1.2	4.5	6	6.3	p > 0.001*
	Chemical								
	AKI	no	37	4.5	1	3.9	4.1	4.7	Z -1.220;
		yes	7	4.5	0.8	4.2	4.7	5.1	p 0.22
	Total								
	AKI	no	119	4.2	0.8	3.7	4	4.6	Z -3.588;
		yes	21	5.1	1.1	4.2	5	6.1	p > 0.01*
Ca	Psychoactive								
	AKI	no	82	2.3	0.3	2.2	2.2	2.4	Z - 2.760;
		yes	14	2.1	0.2	2	2.1	2.2	p 0.006*
	Chemical								
	AKI	no	37	2.32	0.27	2.150	2.400	2.485	Z -1.141;
		yes	7	2.26	0.17	2.100	2.290	2.390	P 0.25
	Total								
	AKI	no	119	2.3	0.3	2.2	2.3	2.4	Z 4.277;
		yes	21	2.1	0.2	2.1	2.1	2.3	P 0.008*

AST	Psychoactive								
	AKI	no	82	76.9	140.5	24	36.5	59.3	Z 5.6576;
		yes	14	990.9	669.2	733	822	1171	p 0.00001*
	Chemical								
	AKI	no	37	81.9	161.3	25.5	34	64.1	Z 0.9787;
		yes	7	344.5	556.8	29	38.7	804.6	p 0.3277
	Total								
	AKI	no	119	78.4	146.6	25	36	61.8	Z 5.1646;
		yes	21	775.4	694	79	778.6	1052	p 0.00001*
ALT	Psychoactive								
	AKI	no	82	56.3	162.1	17	24.6	38	Z 5.5901;
		yes	14	734.1	952.4	182	353	632	p 0.00001*
	Chemical								
	AKI	no	37	68.6	116.1	21	26	54	Z 0.0481;
		yes	7	813.1	1950.3	15	26	294.1	p 0.9616
	Total								
	AKI	no	119	60.1	149	17.4	25	41.6	Z 4.6861;
		yes	21	760.5	1316.1	99	294.1	533.3	p 0.00001*
CK	Psychoactive								
	AKI	no	82	1850.1	3186.8	338.9	709.5	1701	Z 5.6368;
		yes	14	38522.1	34806.9	15146.5	34227.2	42670	p 0.00001*
	Chemical								
	AKI	no	37	2782.7	8541.1	339.6	491.1	1119.5	Z 0.2086;
		yes	7	891.6	1105	465.5	517.2	780	p 0.8348
	Total								
	AKI	no	119	2140.1	5423.6	338.9	633	1492	Z 4.2747;
		yes	21	25978.6	33440.5	780	15146.5	42670	p 0.00002*
hs-troponin I	Psychoactive								
	AKI	no	78	15.3	59.2	1.3	2.2	5.8	Z 4.3535;
		yes	14	121.2	165.1	8.3	62.5	121.3	p 0.00001*
	Chemical								
	AKI	no	35	12.4	26.1	1.4	3.6	7.2	Z 2.8014;
		yes	5	65.6	39.8	46.4	81	94.5	p 0.0051*
	Total								
	AKI	no	113	14.4	51.2	1.3	2.7	6.3	Z 5.1180;
		yes	19	106.6	143.7	8.3	67	101	p 0.00001*
MyogJobin	Psychoactive								
	AKI	no	80	754.2	1565.4	123	160.5	539.9	Z 4.3098;
		yes	13	2461	2549.3	1003	1336.9	1972	p 0.00002*
	Chemical								
	AKI	no	35	257.3	280	126.8	138.9	291.1	Z 1.5826;
		yes	7	323.5	208.1	142.4	314	586.6	p 0.1127
	Total								
	AKI	no	115	603	1332	123.3	154	376.6	Z 4.2768;
		yes	20	1712.9	2283.1	318.3	1001.5	1408	p 0.00002*

AKI – acute kidney injury; AST – aspartate aminotransferase; ALT – alanine aminotransferase; CK – creatine kinase; hs-troponin I – high-sensitivity troponin I; BUN – blood urea nitrogen;
Mann–Whitney U test Z;
*significant for $p < 0.05$

DISCUSSION

The most serious complication of RML is AKI, which in our analysis is present in 15% of patients with acute intoxication. This is in accordance with a previously published study which indicates a prevalence of AKI of 5–30% in patients with RML [9].

In a study by Mousavi et al. [10], the prevalence of AKI was 15% of 114 patients acutely intoxicated with RML, which is compatible with our results. The prevalence of AKI in acute intoxication with RML was 37.1% in the retrospective study by Rogliano et al. [11]. In patients with RML acutely intoxicated, the prevalence of AKI was 16.8%, according to a group of authors [12]. Possible explanations for this discrepancy are methodological differences.

The prevalence of AKI is significantly higher in psychotropic compared to chemical intoxications. AKI in patients intoxicated with psychotropic substances is registered in overdose with heroin – 60%, methadone – 40%, followed by antipsychotics – 25%, anticonvulsants – 17.7%, and antidepressants – 8.3%. In chemical intoxications, AKI is registered in 15.9% of patients. The prevalence of AKI is the

Table 4. Renal replacement therapy and selected parameters by type of intoxication

Type of intoxication			Renal replacement therapy		p
			No – N (%)	Yes – N (%)	
Psychotropic		N (%)	87 (90.63)	9 (9.38)	Fisher's exact test: p 0.9571
Chemical		N (%)	40 (90.91)	4 (9.09)	
Total		N (%)	127 (90.91)	13 (9.29)	
CK	Psychotropic	$\bar{X} \pm SD$	3413 ± 10726	43786 ± 34398.2	Z -4.7325; p 0.00002*
		Min/Max	51/93950	10776/22357	
		Median (IQR)	753 (446–753)	42670 (22357–42670)	
	Chemical	$\bar{X} \pm SD$	2602.1 ± 8231.4	1280.3 ± 1386.4	Z -1.0614; p 0.2885
		Min/Max	65.4/45404	474/3350	
		Median (IQR)	478.3 (321.5–1111.9)	648.6 (495.6–2065)	
	Total	$\bar{X} \pm SD$	3157.7 ± 9981.9	30707.3 ± 34731	Z -4.1176; p 0.00004*
		Min/Max	51/9395	474/129077	
		Median (IQR)	634 (339.6–1532)	22357 (3350–42670)	
Myoglobin	Psychotropic	$\bar{X} \pm SD$	778.9 ± 1527.7	3265.9 ± 2996.8	Z -3.6583; p 0.0002*
		Min/Max	54.3/7213	954/7676	
		Median (IQR)	186.2 (12.7–568.4)	1308.5 (1018.5–421.5)	
	Chemical	$\bar{X} \pm SD$	252.8 ± 269.8	415.8 ± 231.5	Z -1,6068; p 0,1081
		Min/Max	82.7/1467	132.2/622	
		Median (IQR)	140.7 (126.8–291.1)	454.5 (227.4–604.3)	
	Total	$\bar{X} \pm SD$	616.3 ± 1299.5	2315.9 ± 2774.7	Z -3.8078; p 0.0001*
		Min/Max	54.3/7213	132.2/7676	
		Median (IQR)	155.3 (126.8–425.2)	1018.5 (604.3–3741.5)	
hs-troponin I	Psychotropic	$\bar{X} \pm SD$	21.7 ± 79.5	122.4 ± 139.8	Z -3.614; p 0.0003*
		Min/Max	0.3/515	1.5/299.1	
		Median (IQR)	2.3 (1.3–6.8)	73.4 (19.9– 121.3)	
	Chemical	$\bar{X} \pm SD$	15.2 ± 28.3	66.9 ± 53.5	Z -1.977; p 0.0481*
		Min/Max	0.6/138.4	5.2/101	
		Median (IQR)	3.7 (2.2–8.2)	94.5 (5.2–101)	
	Total	$\bar{X} \pm SD$	19.6 ± 67.9	108.5 ± 123.9	Z -4.1003; p 0.00004*
		Min/Max	0.3/515	1.5/399.1	
		Median (IQR)	3.1 (1.3–6.9)	83.9 (14.1–111.1)	

hs-troponin I – high-sensitivity troponin I;
Mann–Whitney U test Z;
*significant for $p < 0.05$

highest in ethylene glycol (100%) and herbicides (33.3%), followed by insecticides (20%), and corrosives (16.7%).

The most common cause of AKI in patients with RML acutely intoxicated is opioid overdose, according to one study by a group of authors [12]. These observations are in line with ours. We found significantly higher presentation of AKI in poisoning with heroin, methadone, in the psychotropic group. According to a group of authors, AKI is associated with a higher rate of opioid and cocaine use in patients with RML [13]. Rogliano et al. [11] reported that overdoses with beta-blockers, calcium-channel inhibitors, acetaminophen, colchicine, lithium, angiotensin-converting enzyme inhibitors / angiotensin II-receptor-blockers were significantly associated with an increased risk of AKI in poisoned patients with RML.

RML is not the only cause of AKI in acutely intoxicated patients, unlike RML resulting from trauma. According to our analysis, patients intoxicated with chemicals who developed AKI were in the group with mild to moderate RML depending on the CK value. AKI in intoxications with ethylene glycol, insecticides, and concentrated acetic acid is due to their nephrotoxic action. Metabolites in ethylene glycol poisoning such as oxalic acid are responsible for the associated end-organ injury, nephrotoxicity. Oxalic acid deposits in renal tubules as insoluble calcium oxalate monohydrate, leading to proximal tubular necrosis. The exact mechanism in organophosphate poisoning is unknown but it may be multifactorial, including direct renal toxicity, or secondary to dehydration/hemodynamic instability causing renal hypoperfusion, or seizure and muscular fasciculation-related RML [14]. Coma, shock, hemolysis, and anuric kidney injury have been reported with poisoning with acetic acid [15].

The results indicate that certain toxic agents in acutely intoxicated patients with RML may play an important role in the development of AKI. We found that patients with AKI acutely intoxicated with RML as well as those intoxicated with psychotropic substances had significantly higher values for creatine, blood urea nitrogen, Na, K, Ca, CK, AST, ALT, troponin, and myoglobin compared with those without AKI. Compatible findings of our analysis are found in the study by Mousavi et al. [10], for a significant positive correlation between serum creatinine values and CK values. Regarding the increased risk of developing

Table 5. Etiological agents in poisoned patients who developed rhabdomyolysis with vs. without acute kidney injury (AKI)

Agents	AKI No		AKI Yes		Adjusted residuals
	N	%	N	%	
Benzodiazepine	20	16.81	0	0	-2*
Neuroleptics	9	7.56	3	14.29	1
Anticonvulsants	5	4.2	1	4.76	0.1
Antidepressants	11	9.24	1	4.76	-0.7
Antiparkinsonic	2	1.68	0	0	-0.6
Heroin	2	1.68	3	14.29	2.9*
Methadone	9	7.56	6	28.57	2.9*
Amphetamine	4	3.36	0	0	-0.9
Cocaine	1	0.84	0	0	-0.4
Tramadol	3	2.52	0	0	-0.7
Ethyl alcohol	15	12.61	0	0	-1.7
Cannabis	1	0.84	0	0	-0.4
Other	1	0.84	0	0	-0.4
Calcium-channel inhibitor	2	1.68	0	0	-0.6
herbicides	2	1.68	1	4.76	0.9
CO	7	5.88	0	0	-1.1
Other gases	1	0.84	0	0	-0.4
Gasoline	2	1.68	0	0	-0.6
Ethylene glycol	0	0	1	4.76	2.4*
Insecticides	12	10.08	3	14.29	0.6
Corrosive agents	10	8.4	2	9.52	0.2
Total	119	100	21	100	-

Table 6. Predictive parameters for developing acute kidney injury in patients with rhabdomyolysis

Parameters	B	S.E.	Sig.	OR	95% CI for OR	
					Lower	Upper
Creatinine	0.048	0.016	0.003	1.049	1.016	1.083
CPK	0.000	0.000	0.180	1.000	1.000	1.000
Sex	-0.993	1.196	0.406	0.371	0.036	3.859
Age	0.046	0.038	0.230	1.047	0.971	1.128
Substance (P/Ch)	-1.043	0.970	0.282	0.352	0.053	2.360
Constant	-8.669	2.983	0.004	0.000		

CPK – creatine phosphokinase

complications such as AKI, similar findings were found in the study by Pajoum et al. [16]. Eizadi-Mood et al. [17] in the prospective study indicated that a CK value > 10,000 IU/L was associated with a higher complication rate and could be an acceptable predictor of outcome in intoxicated patients. In a retrospective study by Nielsen et al. [18], on patients with RML, elevated initial CK values were associated with an increased risk of AKI. In trauma patients, admission myoglobin better predicted AKI than admission CK [19]. Regarding the group with chemical intoxications, we found that patients with AKI have insignificantly higher values for AST, ALT, and troponin compared to those without AKI. CK and myoglobin values in this group were insignificantly higher in patients with AKI compared to those without AKI. We found that serum creatinine on admission in both groups is a predictor of AKI. According to the study by Rogliano et al. [11], serum creatinine ≥ 125 µmol/L on admission was the highest predictive variable for AKI in poisonings.

Recommendations to lower the risk of AKI in patients with RML include fluids to correct hypovolemia, achieve adequate diuresis with a goal urine output of 300 mL/h, and even dilute the released toxic endogenous metabolites, despite their relatively low level of evidence [2]. Bicarbonate, mannitol, and loop diuretics are not strong evidence for improved outcomes [2].

The need for RRT in our analysis in patients acutely intoxicated with RML is 9.3%. Intermittent RRT was used in our patients with RML due to acute intoxication with psychotropic and chemical substances. RRT was initiated two or three days after admission and our patients required one hemodialysis session.

According to the literature, the need for RRT in patients with RML ranges 4–20% [20]. The prevalence of RRT is significantly higher in psychotropic compared to chemical intoxications. In acutely intoxicated patients with RML and in the group with psychotropic intoxications, the level of CK on the first day is significantly higher in patients who need RRT compared to those who do not need this therapy, and in the group of chemical intoxications, this difference is insignificant. Eizadi-Mood et al. [17] in their study reported that in acutely intoxicated patients with coma increased CK values were associated with an increased need for dialysis. According to a study by Dadpour et al. [21], approximately 80% of patients with serum CK levels < 10,000 IU/L required dialysis. In contrast to our results, the study by Pajoum et al. [16] presents that there is no significant correlation between CK levels and the need for dialysis. Stopping RRT depends on multiple factors: resolution of the underlying cause, creatine level and the option of being managed effectively using other therapies (e.g., furosemide for fluid balance) [22]. In most patients with RML, renal function is restored within a few months [23, 24].

The limitation of the study is the small number of patients with RML as a result of acute intoxication. The small number of patients with AKI in most of the different types of poisoning limited the possibility of performing standard *post hoc* test for each of the used substances for poisoning. Urine output, which is an important clinical parameter, is missing.

CONCLUSION

The prevalence of AKI and the necessity of RRT was significantly higher in psychotropic intoxication compared to chemical intoxication. Certain toxic agents in acutely intoxicated patients with RML may have an important role in the development of AKI. Serum creatinine on admission in acute intoxication is a predictor of AKI. In the group of psychotropic intoxications, RRT was used in overdoses with heroin, methadone, and antipsychotics, while in the chemical group it was used in those intoxicated with ethylene glycol, herbicides, insecticides, and corrosive agents. The level of high-sensitivity troponin I in both psychotropic and chemical group are significantly higher in patients who need RRT compared to those who do not need this therapy. Larger cohorts are needed to improve our findings.

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Акутно оштећење бубрега и неопходност терапије замене функције бубрега код акутно интоксираних болесника са рабдомиолизом

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САЖЕТАК

Увод/Циљ Ово истраживање је имало за циљ да анализира карактеристике селективних параметара повезаних са настанком акутног оштећења бубрега и неопходношћу терапије замене функције бубрега код болесника са рабдомиолизом услед акутне интоксикације психотропним и хемијским супстанцама у прва 24 часа.

Методе У клинички контролисаној проспективној студији, 140 болесника са рабдомиолизом подељено је у две групе у зависности од супстанце која је изазвала интоксикације – психотропне или хемијске. Болесници су одабрани према унапред одређеним критеријумима за укључивање и искључивање.

Резултати Акутно оштећење бубрега јавило се код 15% од 140 болесника са рабдомиолизом, од којих је 14 (66,7%) имало психотропну интоксикацију, а седам (33,3%) хемијску интоксикацију. Статистичка анализа је показала значајно већу преваленцију у групи са психотропном интоксикацијом у односу на ону са хемијском интоксикацијом ($p = 0,0002$). Вредности креатин киназе за средњу вредност интерквартилног распона код болесника без терапије и са терапијом замене функције бубрега биле су у случају психотропних супстанци 753 (446–753) наспрам 42.670 (22.357–42.670) *U/L*, док су за хемијске супстанце износиле 478,3 (321,5–1111,9) наспрам 648,6 (495,6–2065) *U/L*. Код психотропне интоксикације ова разлика је била значајна ($p = 0,00002$), док је код хемијске незнатна ($p = 0,288$). Терапија замене функције бубрега је спроведена код 13 (9,3%) болесника са рабдомиолизом, од којих је девет (69,2%) било са психотропном интоксикацијом, а четири (30,8%) болесника са хемијском интоксикацијом.

Закључак Преваленција акутног оштећења бубрега и потреба за терапијом замене функције бубрега биле су значајно веће код психотропне интоксизације у поређењу са хемијском интоксикацијом. Ниво креатин киназе и миоглобина првог дана код болесника са психотропном интоксикацијом, и високо осетљиви тропонин I у обе групе болесника – са психотропном и хемијском интоксикацијом – значајно су већи код болесника којима је неопходна терапија замене функције бубрега у односу на оне којима ова терапија није потребна.

Кључне речи: токсичност; креатин киназа; миоглобин