folia medica

Folia Medica 65(3):407-414
DOI: 10.3897/folmed.65.e81145

Original Article

Comparison of Rhabdomyolysis in Acutely Intoxicated Patients with Psychotropic and Chemical Substances

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Received: 28 Jan 2022 ♦ **Accepted:** 24 Mar 2022 ♦ **Published:** 30 June 2023

Citation: Babulovska A, Caparovska D, Stefanovska VV, Simonovska N, Pereska Z, Petkovska L, Kostadinoski K, Naumoski K. Comparison of rhabdomyolysis in acutely intoxicated patients with psychotropic and chemical substances. Folia Med (Plovdiv) 2023;65(3):407-414. doi: 10.3897/folmed.65.e81145.

Abstract

Introduction: Rhabdomyolysis is characterized by a muscle injury that leads to the release of intracellular muscle contents/constituents into the systemic circulation.

Aim: We examined the association between the severity of the clinical presentation and creatinine phosphokinase values in patients with rhabdomyolysis acutely intoxicated with psychotropic and chemical substances.

Materials and methods: This clinically controlled prospective study included 140 patients with rhabdomyolysis hospitalized at the University Clinic of Toxicology in 2019. They were divided into two groups by the substance used for intoxication (psychotropic or chemical).

Results: On the third day of hospitalization, we found a significant association between the type of intoxication and the degree of rhabdomyolysis according to the poisoning severity score (p=0.0256). The significance was due to intoxications with neuroleptics – 50% (n=6), anticonvulsants – 20% (n=1), antidepressants – 16.67% (n=2), heroin – 25% (n=1), and methadone – 54% (n=6). According to the poisoning severity score, the majority of intoxicated patients with chemical substances – other gases 100% (n=1), and those intoxicated with psychotropic substances – methadone 46.67% (n=7), neuroleptics 42.67% (n=5), heroin 40% (n=2), antidepressants 8.33% (n=1), had severe rhabdomyolysis. In psychotropic intoxications, creatine kinase had a significant linear positive weak correlation with mortality (p=0.0234).

Conclusions: Rhabdomyolysis and its clinical symptoms and signs were significantly more common in patients intoxicated with psychotropic substances compared to chemical intoxications. Intoxicated patients with psychotropic substances had more severe rhabdomyolysis on the third day of hospitalization. In psychotropic intoxication, with increasing creatine kinase level on the first day there was a significant increase in mortality.

Keywords

creatine kinase, intoxication, mortality, rhabdomyolysis, poisoning severity score

INTRODUCTION

Rhabdomyolysis is characterized by muscle injury that leads to the release of intracellular muscle contents/constituents into the systemic circulation. Muscle injuries from any cause can lead to rhabdomyolysis, and hence, there are numerous causes including trauma or muscle compression as well as non-traumatic causes.[1] Many cases of rhabdomyolysis are not detected; the exact incidence of rhabdomyolysis is unknown, and very mild cases of rhabdomyolysis tend to go unrecognized. Poisoning has been known as a major cause for emergency department (ED) admission in developing countries and is responsible for a considerable rate of morbidity and mortality.[2] It could be followed by various complications such as rhabdomyolysis.[3] More recently, 81% of cases of rhabdomyolysis have been due to the use of drugs and alcohol.[4] Drug-induced rhabdomyolysis can be divided into primary and secondary myotoxic effects. Primary toxic-induced rhabdomyolysis is caused by direct damage to the myocyte function and integrity. The secondary effects of toxins are due to certain predisposing risk factors such as local compression of muscles during coma, prolonged seizures, trauma, and metabolic abnormalities.[4] The classic presentation of this condition is muscle pain, weakness, dark tea-colored urine (pigmenturia), and a marked elevation of serum creatine kinase (CK) five to ten times above the upper limit of normal serum levels.[5]

AIM

The aim of this study was to determine the association between the severity of the clinical presentation and creatinine phosphokinase values in rhabdomyolysis patients acutely intoxicated with psychotropic and chemical substances.

MATERIALS AND METHODS

Materials

This was a clinically-controlled prospective study. It included 140 patients with rhabdomyolysis divided into two groups by the substance they used for intoxication (psychotropic or chemical). The patients were hospitalized at the University Clinic of Toxicology in Skopje in 2019. Rhabdomyolysis was defined as creatine phosphokinase (CK) >250 U/L. We included adult patients ≥18 years of age with rhabdomyolysis, acutely intoxicated with psychotropic and chemical substances in the first 48 hours. We excluded patients with rhabdomyolysis caused by muscle trauma as a result of a traumatic incident, myocardial infarction, cerebral vascular infarction, or cerebral hemorrhage, and chronic renal disease. The study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje.

Methods

According to the Poison Severity Score (PSS) based on CK values, all patients with rhabdomyolysis were divided into 3 groups: a) those with mild rhabdomyolysis (mild pain and tenderness, and CK>250-≤500 U/L; b) those with moderate rhabdomyolysis (pain, rigidity, cramps, and fasciculation, CK>1,500-≤10,000 U/L); and c) those with severe rhabdomyolysis (intense pain, extreme rigidity, extensive cramping and fasciculation, rhabdomyolysis with complications, CK>10,000 U/L, compartment syndrome). We analyzed both groups of patients with psychotropic and chemical intoxications, according to PSS, at 1, 3, and 5 days during hospitalization.

Statistical analysis

The data obtained in the study were analyzed using SPSS, version 22.0. The chi-square and Fisher's exact tests were used to determine the association between certain features in the group of subjects. Mann-Whitney U test were used to compare average values according to distribution. Values of $p<0.05$ were considered statistically significant.

RESULTS

During the study period, 1446 patients with a diagnosis of intoxication were treated at the University Clinic of Toxicology in Skopje. Of these patients, 140 had rhabdomyolysis. Intoxication with psychotropic substances had 96 (68.6%) patients with rhabdomyolysis, while 44 (31.4%) had intoxication with a chemical substance. Intoxications with psychotropic substances were significantly more frequent than the intoxications with chemical substances (difference 37.14%, 95% CI (25.7, 47.2); $\chi^2=38.485$; df=1; $p<0.001$). Male versus female ratio in the group with psychotropic intoxications was 71 (74%) vs. 25 (26%), while in the group with chemical intoxications 34 (77.3%) vs. 10 (22.7%). There was no significant association between the gender of patients with rhabdomyolysis and the type of intoxication (Pearson chi-square test=0.177; df=1; $p=0.674$). In the group with psychotropic or chemical intoxications, the average age of patients with rhabdomyolysis was 39.2±13.4, with min/max 18/73 years vs. 46.9±15.2, with min/max 18/80 years, respectively. Fifty percent of patients in the group with psychotropic intoxications were under the age of 38 for median IQR=38 (29-45), while in the group with chemical intoxications 50% were under the age of 52 for median IQR=52 (36-59). The analysis showed significantly older patients in the group with chemical intoxications than in the group with psychotropic intoxications (Mann-Whitney U test: Z=–2.883; $p=0.004$).

According to PSS, on the first day there were patients with mild, moderate, and severe rhabdomyolysis as follows: a) whole sample – 97 (69.28%), 27 (19.29%), and 16

(11.43%), respectively; b) psychotropic intoxications – 61 (63.54%), 20 (20.83%), and 15 (15.63%), respectively; and c) chemical intoxications – 36 (81.82%), 7 (15.91%), and 1 (2.27%), respectively. On the first day of hospitalization, we found no significant association between the type of intoxication and degree of rhabdomyolysis according to PSS score (Fisher exact test: p=0.133). According to PSS, on the third day there were patients with mild, moderate and severe rhabdomyolysis as follows: a) whole sample – 39 (45.3%), 30 (34.9%), and 17 (19.8%), respectively; b) psychotropic intoxications 23 (40.4%), 18 (31.6%), and 16 (28.1%), respectively; and c) chemical intoxications 16 (55.2%), 12 (41.4%), and 1 (3.6%), respectively. On the third day of hospitalization, we found a significant association between the type of intoxication and degree of rhabdomyolysis according to PSS score (Fisher exact test: p=0.026). The probability of severe rhabdomyolysis on the third day was 10,927 times (OR=10,927, 95% CI 1.37, 87.17) (p=0.006) significantly higher in patients with psychotropic intoxications than in those with chemical intoxications. Additional analysis made on the third day showed that this significance was due to intoxications with neuroleptics – 6 (50%), anticonvulsants – 1 (20%), antidepressants – 2 (16.67%), heroin – 1 (25%) and methadone – 6 (54%). According to PSS, on the fifth day, there were patients with mild, moderate and severe rhabdomyolysis as follows: a) whole sample – 26 (57.8%), 16 (35.6%), and 3 (6.7%), respectively; b) psychotropic intoxications – 14 (48.3%), 12 (41.4%), and 3 (10.3%), respectively; and c) chemical intoxications – 12 (75%), 4 (25%), and 0 (0.0%), respectively. On the 5th day of hospitalization, we found no significant association between the type of intoxication and the status of mild/moderate rhabdomyolysis according to PSS score (Fisher exact test: p=0.157). Severe rhabdomyolysis according to PSS score was found in three patients with psychotropic intoxication and in none with chemical intoxication **(Table 1)**.

In all patients with rhabdomyolysis, we performed an analysis according to PSS and etiological cause of intoxication on the first day of hospitalization **(Table 2)**. The analysis showed that most patients with severe rhabdomyolysis were intoxicated with chemical substances – other gases – 1 (100%), psychotropic substances – methadone – 7 (46.67%), neuroleptics – 5 (42.67%), heroin – 2 (40%), antidepressants -1 (8.33%). Moderate rhabdomyolysis was observed due to intoxication with psychotropic substances; antiparkinsonian drugs – 1 (50%), heroin – 2 (40%), methadone – 6 (40%), ethyl alcohol – 3 (20%), anticonvulsants – 1 (16.67 %), antidepressants – 2 (16.67), benzodiazepines – 3 (15%), carbon monoxide (CO) – 3 (42.86%), neuroleptics – 1 (8.33%), in the group of intoxication with chemical substances moderate rhabdomyolysis was present; mushrooms – 1 (33.33%), corrosives -2 (16.67%), pesticides – 1 (6.67%). Mild rhabdomyolysis was found in intoxication with psychotropic substances; amphetamines – 4 (100%), cocaine – 1 (100%), tramadol – 3 (100%), other drugs – 2 (100%), cannabis – 1 (100%), others – 1 (100%), benzodiazepines – 17 (85%), anticonvulsants – 5 (83.33%), ethyl alcohol -12 (80%), antidepressants – 9 (75%), neuroleptics – 6 (50%), heroin – 1 (20%), methadone – 2 (13.33). In the group of chemical intoxications, rhabdomyolysis was found in gasoline – 2 (100%), ethylene glycol – 1 (100%), pesticides – 14 (93.33%), corrosives – 10 (83.33%), mushrooms – 2 (66.67%), carbon monoxide – 4 (57.14%). The distribution of patients with rhabdomyolysis according to PSS and etiological cause on the first day of hospitalization is given in **Table 2**.

Patients in both groups according to type of intoxication, psychotropic or chemical, were analyzed for clinical symptoms at admission (muscle pain, muscle weakness, and colored urine) **(Table 3)**.

Out of the total number of patients, muscle pain was present in 15 (10.7%) patients with rhabdomyolysis, 12 (12.5%) in those intoxicated with psychotropic substanc-

Table 1. Patients with rhabdomyolysis according to Poison Severity Score and type of intoxication at three time points

Poison Severity Score		Type of intoxication			p
		Psychotropic N (%)	Chemical N (%)	Total N (%)	
1 day	Mild	61 (63.54)	36 (81.82)	97 (69.28)	Fisher exact test: p=0.133
	Moderate	20 (20.83)	7 (15.91)	27 (19.29)	
	Severe	15 (15.63)	1 (2.27)	16 (11.43)	
3 day	Mild	23 (40.4)	16 (55.2)	39 (45.3)	Fisher exact test: p=0.026*
	Moderate	18 (31.6)	12 (41.4)	30 (34.9)	
	Severe	16 (28.1)	1 (3.6)	17 (19.8)	
5 day	Mild	14 (48.3)	12 (75.0)	26 (57.8)	mild/moderate Fisher exact test: p=0.157
	Moderate	12 (41.4)	4 (25.0)	16 (35.6)	
	Severe	3 (10.3)	0 (0.00)	3 (6.7)	

* significant at p<0.05

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Table 2. Distribution of patients with rhabdomyolysis according to Poison Severity Score and etiological agent on the first day of hospitalization

Ethological agents		Poison Severity Score - PSS						Total
		Mild		Moderate		Severity		
		N	(%)	N	(%)	N	(%)	
1	Benzodiazepine	17	85.00	3	15.00	0	0.00	20
2	Antipsychotic	6	50.00	1	8.33	5	42.67	12
3	Anticonvulsants	5	83.33	1	16.67	0	0.00	6
4	Antidepressants	9	75.00	2	16.67	1	8.33	12
5	Antiparkinsons	1	50.00	1	50.00	0	0.00	2
6	Other medication	2	100.00	0	0.00	0	0.00	2
7	Pesticides	14	93.33	1	6.67	0	0.00	15
8	Corrosive agents	10	83.33	2	16.67	0	0.00	12
9	Heroin	1	20.00	2	40.00	2	40.00	5
10	Methadone	2	13.33	6	40.00	7	46.67	15
11	Amphetamine	4	100.0	0	0.00	0	0.00	4
12	Cocaine	1	100.0	0	0.00	0	0.00	1
13	Ecstasy	-	-	-	-	-	-	-
14	Tramadol	3	100.0	0	0.00	0	0.00	3
15	Ethyl alcohol	12	80.00	3	20.00	0	0.00	15
16	Mushrooms	2	66.67	1	33.33	0	0.00	3
17	Carbon monoxide	4	57.14	3	42.86	0	0.00	7
18	Petroleum distillate	0	0.00	0	0.00	1	100.0	1
19	Gasoline	2	100.0	0	0.00	0	0.00	2
20	Ethylene glycol	1	100.0	0	0.00	0	0.00	1
21	Others	1	100.0	0	0.00	0	0.00	1
22	Cannabis	1	100.0	0	0.00	0	0.00	1
Total		98	70.0	26	18.57	16	11.43	140 (100%)

Table 3. Patients with rhabdomyolysis by type of intoxication and clinical symptoms

Clinical symptoms		Type of intoxication			*p*
		Psychotropic N (%)	Chemical N (%)	Total N (%)	
Muscle pain	no	84 (87.50)	41 (93.18)	125 (87.29)	Fisher exact test: p=0.313
	yes	12 (12.50)	3 (6.82)	15 (10.71)	
Muscle weakness	no	83 (86.46)	40 (90.91)	123 (87.86)	Fisher exact test: p=0.454
	yes	13 (13.54)	4 (9.09)	17 (12.14)	
Pigmented urine	no	83 (86.46)	44 (100)	127 (90.71)	
	yes	13 (13.54)	0 (0.00)	13 (9.29)	

* significant for $p<0.05$

es, and in three patients (6.82%) intoxicated with chemical substances **(Table 3)**. The analysis showed no significant association between muscle pain and type of intoxication (Fisher exact test: p=0.313).

We registered muscle weakness in 17 (12.1%) patients with rhabdomyolysis **(Table 3)**. According to the type of intoxication, we noticed the presence of muscle weakness in 13 (13.5%), 4 (9.1%) of those intoxicated with psychotropic, chemical substances, without significant association between muscle weakness and type of intoxication (Fisher exact test: p=0.454).

Mortality (Mt) was registered in 13 (9.3%) patients with

rhabdomyolysis, of which 3 (23.1%) with psychotropic intoxication and 10 (76.9%) with chemical intoxication. The analysis indicated a significantly lower mortality in psychotropics compared to chemical intoxications (difference 46.1%, 95% CI 28.7, 59.8; χ^2=27.137; df=1; p<0.001).

DISCUSSION

The severity of rhabdomyolysis (mild, moderate, and severe) was determined using the Poisoning Severity Score (PSS), with CK as the primary parameter in patients intoxicated with psychotropic/chemical substances. Psychotropic intoxications were present in 64.58% vs. 19.79% vs. 15.63%, and chemical intoxications in 79.55% vs. 15.91% vs. 4.55% of patients, respectively. In the study of Janković et al., most of the patients were in the first group with mild, and the least in the group with severe rhabdomyolysis, which was in accordance with our results.[6] In the Eizadi-Mood et al. study, most of the patients who arrived in a coma, depending on the CK value, were in the group with moderate (55%), and the least (20%) in the group with severe rhabdomyolysis.[7] Certain differences found between their and our study may be due to our criterion in the selection of patients acutely intoxicated with rhabdomyolysis.

In the group of psychotropic intoxications, rhabdomyolysis was most often present in intoxications with benzodiazepines, which according to PSS were present in the groups with mild and moderately increased CK values. Benzodiazepines cause rhabdomyolysis as a result of prolonged immobility in prolonged disturbance of consciousness, leading to local compression and muscle ischemia.[8] Ethyl alcohol intoxications were also present in the group with mild and moderate rhabdomyolysis. Ethyl alcohol can cause rhabdomyolysis through its direct toxic effects and through side effects related to altered mental status, impaired consciousness, and coma, with prolonged immobilization and muscle compression.[9] Patients intoxicated with selective serotonin reuptake inhibitors were more common in the mild group compared with the moderate rhabdomyolysis group. Rhabdomyolysis in these patients occurs secondary to prolonged immobilization, convulsions, serotonin toxicity, and hyperthermia.[10,11] Patients suffering from severe agitation, excessive muscle activity, or hyperthermia as a result of amphetamine and cocaine abuse are at risk of developing rhabdomyolysis.[12,13] Such patients in our study were in the group with mild rhabdomyolysis. Patients with tramadol overdose were also in the group with a mild increase in CK. Rhabdomyolysis in these intoxications occurs through a combination of mechanisms, prolonged immobilization (due to CNS depression), and neuromuscular excitability (serotonin syndrome).

In the group of chemical substances, the most common were those of poisonings with corrosive agents. According to PSS, they were more prevalent in the group with mild to moderate CK values. Rhabdomyolysis in these poisonings was probably due to the release of this enzyme from the damaged muscles of the digestive tract. An increase in CK, mainly with a mild level, was observed in pesticide poisonings, the most common of which was organophosphate poisoning. Organophosphates with CNS toxicity lead to central respiratory depression, agitation, tonic-clonic convulsions, and coma. Muscle damage is also caused by muscle fasciculations caused by the toxic effect of OFS on the neuromuscular junction. Patients intoxicated with CO were in the group with mild to moderate rhabdomyolysis. Carboxyhaemoglobin disrupts the tissues' oxygen supply, leading to muscle ischemia and skeletal muscle necrosis. Mild increases in CK were observed in fungal poisonings with the Amanita phaloides species. Elevated CK values in these poisonings are likely to be part of the severe clinical presentation.

According to our analysis, the most common opioid triggers for rhabdomyolysis were methadone and heroin. According to the level of CK, all three groups included patients with methadone and heroin overdoses, and the largest number was in the group with severe rhabdomyolysis. A methadone overdose can lead to profound CNS depression or coma, with prolonged immobility, leading to ischemia caused by skeletal muscle pressure, resulting in muscle breakdown.[14,15] Complications of prolonged immobilization in heroin overdose include hypothermia, skin necrosis, compartment syndrome, and rhabdomyolysis.[16]

We found that the highest CK value was due to methadone overdose of 129077 U/L in the psychotropic intoxication group versus 45404 U/L in the case of intoxication with other gases in the chemical group. Extremely high CK levels (100,000 U/L or higher) have been reported in patients overdosed on methadone, heroin, or morphine.[17,18] In the study of Taheri et al., the highest value of this serum marker was 34,000 U/L[19], and in the Melli et al.'s study – 250,000 U/L[20]. In a retrospective study, the most common cause of severe rhabdomyolysis was prolonged immobilization due to substance abuse.[21] The study of Laprin et al. showed severe rhabdomyolysis to be a common complication in 11.7% of opiate overdose patients.[22] According to our analysis, the reason for severe rhabdomyolysis was the poisoning with antipsychotics and tricyclic antidepressants. Rhabdomyolysis after overdose with an antipsychotic drug may occur as a consequence of prolonged immobility, excessive muscle rigidity, or activity or convulsions.[23,24] One patient had neuroleptic malignant syndrome (NMS) in the severe RM group. NMS may be associated with excessive muscle activity or rigidity followed by an increase in serum CK levels.[25] Rhabdomyolysis is one of the diagnostic criteria for NMS. In tricyclic antidepressant (TCA) poisoning, rhabdomyolysis occurs in patients with prolonged coma-related immobilization, excessive muscle activity/convulsions, or hyperthermia.[26] In the group of intoxication with chemical substances, the causes of severe rhabdomyolysis are other gases. The cause of rhabdomyolysis in these intoxications is prolonged immobilization and convulsions.[27]

According to our analysis, 10.7% of patients with rhabdomyolysis, 12.5% of those intoxicated with psychotropic

substances, and 6.82% of those intoxicated with chemical substances were with muscle pain. No significant association was found between muscle pain and the type of intoxication. Muscle weakness was registered in 12.1% of patients with rhabdomyolysis. The presence of muscle weakness was observed in 13.5%, i.e., 9.1% of those intoxicated with psychotropic, i.e., chemical substances, without significant association between muscle weakness and type of intoxication. Pigmented urine was present in 13.5% of patients, all from the group with rhabdomyolysis after intoxication with psychotropic substances. We did not register the presence of pigmented urine in any of the patients with rhabdomyolysis due to chemical intoxication. The clinical symptoms of muscle pain, muscle weakness, and pigmented urine, according to our analysis, were more common in the group intoxicated with psychotropic substances. These results showed that a small percentage of patients with rhabdomyolysis developed clinical signs, indicating potential oversights that may be made during the admission triage of these patients. According to some authors, 12% of patients with rhabdomyolysis had muscle weakness, 8.33% had myalgia, and 29.16% myoglobinuria.[28] The reason for the lower prevalence of muscular symptoms and signs can be explained by the disturbance of consciousness in acutely intoxicated patients with rhabdomyolysis.

CONCLUSIONS

Rhabdomyolysis was significantly more common in patients intoxicated with psychotropic substances compared to chemical intoxications. Those intoxicated with psychotropic substances had more severe rhabdomyolysis on the third day of hospitalization. Creatine kinase has been shown to be the best marker for the diagnosis and prompt treatment of rhabdomyolysis in patients intoxicated with psychotropic or chemical substances. Clinical symptoms and signs of rhabdomyolysis were not present in all intoxicated patients but were more common in the group intoxicated with psychotropic substances.

Limitation

The generalizability of the results may be limited because this study included only patients who came to our Clinic. Since some of our patients were unconscious at admission, obtaining a reliable history of symptoms and assessment of signs was very difficult.

Acknowledgements

The authors have no support to report.

Funding

The authors have no funding to report.

Competing Interests

The authors have declared that no competing interests exist.

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Сравнение рабдомиолиза у больных с острой интоксикацией психотропными и химическими веществами

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Дата получения: 28 января 2022 ♦ **Дата приемки:** 24 марта 2022 ♦ **Дата публикации:** 30 июня 2023

Образец цитирования: Babulovska A, Caparovska D, Stefanovska VV, Simonovska N, Pereska Z, Petkovska L, Kostadinoski K, Naumoski K. Comparison of rhabdomyolysis in acutely intoxicated patients with psychotropic and chemical substances. Folia Med (Plovdiv) 2023;65(3):407-414. doi: 10.3897/folmed.65.e81145.

Резюме

Введение: Рабдомиолиз характеризуется повреждением мышц, которое приводит к высвобождению внутриклеточного мышечного содержимого/компонентов в системный кровоток.

Цель: Изучить связь между тяжестью клинической картины и показателями креатининфосфокиназы у больных рабдомиолизом, находящихся в состоянии острой интоксикации психотропными и химическими веществами.

Материалы и методы: В данное клинически контролируемое проспективное исследование было включено 140 пациентов с рабдомиолизом, госпитализированных в Университетской токсикологической клинике в 2019 г. Они были разделены на две группы по веществу, использованному для интоксикации (психотропные или химические).

Результаты: На 3-й день госпитализации выявлена достоверная связь между видом интоксикации и степенью рабдомиолиза по шкале оценки тяжести отравления (p=0.0256). Значимость обусловлена интоксикациями нейролептиками – 50% (n=6), антиконвульсантами – 20% (n=1), антидепрессантами – 16.67% (n=2), героином – 25% (n=1), метадоном – 54% (n=6). По шкале оценки тяжести отравления большинство больных в состоянии интоксикации химическими веществами – другими газами 100 % (n=1), психотропными веществами – метадоном 46.67 % (n=7), нейролептиками 42.67 % (n=5), героином 40% (n=2), антидепрессантами 8.33% (n=1), имели тяжёлый рабдомиолиз. При психотропных интоксикациях креатинкиназа имела достоверную линейную положительную слабую корреляцию со смертностью (p=0.0234).

Заключение: Рабдомиолиз, его клинические симптомы и признаки достоверно чаще встречались у больных, находящихся в состоянии интоксикации психотропными веществами, по сравнению с химическими интоксикациями. У больных в состоянии интоксикации психотропными веществами на третий день госпитализации отмечался более выраженный рабдомиолиз. При психотропной интоксикации при повышении уровня креатинкиназы в первые сутки отмечалось значительное увеличение смертности.

Ключевые слова

креатинкиназа, интоксикация, смертность, рабдомиолиз, оценка тяжести отравления