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

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

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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 7 (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 IQR in patients without / with renal replacement therapy were in psychotropic – 753 (446–753) *vs*. 42670 (22357–42670) 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, of which 9 (69.2%) with psychotropic intoxication and 4 (30.8%) 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, and high-sensitivity Troponin I in both groups psychotropic and chemical are significantly higher in patients who need renal replacement therapy compared to those who do not need this therapy.

Keywords: toxicity; creatine kinase; myoglobin

САЖЕТАК

Увод/Циљ Анализа селективних параметара у вези са настанком акутно оштећење бубрега и неопходношћу терапија замене функције бубрега код пацијената са рабдомиолизом услед акутне интоксикације психотропним и хемијским супстанцама у прва 24 часа.

Методе У клинички контролисаној проспективној студији, 140 пацијената са рабдомиолизом подељено је у две групе у зависности од интоксикације тј. психотропна или хемијска. болесници су одабрани према унапред одређеним критеријумима укључивања и искључења.

Резултати Акутно оштећење бубрега јавило се код 15% од 140 пацијената са рабдомиолизом, од којих је 14 (66,7%) била са психотропним, а 7 (33,3%) са хемијским супстанцама. Статистичка анализа је показала значајно повећану преваленцију у психотропној групи у односу на оне са хемијском интоксикацијом (p=0,0002). Вредности креатин киназе за *median IQR* код болесника без терапије и са терапијом замене функције бубрега биле су психотропне – 753 (446–753) наспрам 42670 (22357–42670) U/L; и хемијске – 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 хемијских незнатна (*p* = 0,288). Терапија замене функције бубрега је спроведена код 13 (9,3%) болесника са рабдомиолизом, од чега 9 (69,2%) са психотропном интоксикацијом и 4 (30,8%) са хемијском интоксикацијом.

Закључак Преваленција акутно оштећење бубрега и неопходност терапије замене функције бубрега била је значајно већа код психотропне у односу на хемијске интоксикације. Ниво креатин киназе и миоглобина првог дана у групи са психотропним, и високо осетљивим тропонином И у обе групе психотропних и хемијских је значајно већи код пацијената којима је неопходна терапије замене функције бубрега у односу на оне којима ова терапија није потребна.

Кључне речи: токсичност; креатин киназа; миоглобин

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 rhabdomyolysis 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 (Fe2+) to ferric oxide (Fe3+) [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 acute kidney injury (AKI) are classified into three clinical stages based on increase in creatinine and/or decrease in urine output, according to KDIGO (Kidney Disease Improving Global Outcomes) recommendations [8].

This study aimed to analyze 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

This was a prospective clinical study conducted during 2019 at the University Clinic for Toxicology in Skopje. The study included patients with rhabdomyolysis divided into two groups, depending on the toxic substance consumed by them (psychotropic or chemical). 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 hours prior to admission into 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 Kidney Disease Improving Global Outcomes

(KDIGO) criteria, the AKI was categorized as AKI I, II, III, respectively, based on increase in serum creatinine ≥26.5 μmol/L or increase to ≥ 1.5-fold to twofold 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 by the means of the statistical program SPSS version 22.0. The quantitative data were analyzed in series, using central tendency (mean and median) and dispersion measures (standard deviation and IQR). Fisher's exact test were used to determine the association among certain features in the group of subjects. Mann-Whitney U test were 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 with diagnoses of acute intoxications were treated during the study period at the University Clinic for Toxicology in Skopje, Republic of North Macedonia. Of the total number, 140 patients had developed rhabdomyolysis. Ninety-six (68.6%) patients with rhabdomyolysis had been poisoned with psychotropic drugs, while the other 44 individuals (31.4%) had consumed chemical agents. Intoxications with psychotropic substances were significantly more frequently seen than those with chemical substances.

With AKI were a total of 21 (15%) of patients with rhabdomyolysis, of which 14 (66.7%) with psychotropic intoxication and 7 (33.3%) with chemical intoxication. The analysis indicated a significantly higher prevalence of AKI in psychotropics compared to chemical intoxications (Difference 33.4% [(15.6-48.2) 95% CI]; Chi-square = 13,552; df = 1; p = 0.0002).

Males and females in the group with psychotropic intoxications with AKI were 13 (92.8%) vs. 1 (7.14%), while in the group with chemical intoxications were 3 (42.86%) vs. 4 (57.1%). The average age of patients with rhabdomyolysis in the group with psychotropic, chemical intoxications with AKI, was 39.9 ± 13.4, with min./max. 26/53 years vs. 57.8 ± 15.1, with min./max. 41/82 years respectively. Fifty percent of the patients in the group with psychotropic intoxications were under 40 years of age for Median IQR. = 40 (36-47), while in the group with chemical intoxications 50% were under 54 years of age for Median IQR = 54 (52-65). There was a significantly older patient in the group with chemical intoxications (Mann-Whitney U Test: Z=-3,0597; p=0,002221*) (Table 1).

We analyzed the etiological factors for AKI individually for each of these parameters with reference to the prevalence of psychotropic and chemical parameters (Table 2). In psychotropic intoxications, AKI was present in 14 (14.6%) patients in the group. The prevalence of AKI according to etiological cause was highest in: a) heroin 3 (60%); and b) methadone 6 (40%); followed by c) neuroleptics 3 (25%); d) anticonvulsants 1 (17.7%) and e) antidepressants 1 (8.3%). In chemical intoxications, AKI was reported in 7 (15.9%) patients. The prevalence of AKI by etiological cause was highest 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 were N= 2 (9.53%) patients, stage II N=6 (28.57%) patients, and stage III N=13 (61.90%) patients in need of renal replacement therapy. With renal replacement therapy were a total of 13 (9.3%) patients with rhabdomyolysis, of which 9 (69.2%) with psychotropic intoxication and 4 (30.8%) with chemical intoxication. The analysis showed a significantly higher prevalence of RRT in psychotropics compared to chemical intoxications (Difference 38.4% [(20.7-52.7) 95% CI]; Chi-square = 18,036; df = 1; p = 0.0001). Out of a total of 21 patients diagnosed with AKI, a total of 13 (61.9%) received RRT while 8 (38.1%) did not need 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 highest in: a) heroin 2 (40%); and b) methadone 4 (26.7%); followed by: c) neuroleptics 3 (25%). In chemical intoxications, RRT was applied in 4 (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 AST, ALT, CK, troponin and myoglobin obtained on the first day of hospitalization of patients with rhabdomyolysis (Table 3).

We found that patients with AKI from the whole sample with rhabdomyolysis as well as in psychotropic intoxications had significantly higher values for all selected parameters compared to those without AKI, and the whole sample with rhabdomyolysis had insignificantly higher values for Na (p=0.89) (Table 3). Regarding the group with chemical intoxications, we found that patients with AKI had insignificantly higher values for the parameters Na (p=0.311), K (p=0,22), Ca (p=0.25), AST (p = 0.3277), ALT (p = 0.9616) and hs-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: a) whole sample - 634 (339.6-1532) vs. 22357 (3350-42670) U / L; b) psychotropic - 753 (446-753) vs. 42670 (22357-42670) 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: 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 this difference was significant (p = 0.00002 vs. p = 0.00003), while in the chemical ones it was insignificant (p = 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: 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 in poisoning with benzodiazepines in the psychotropic 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, gender, 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 78.0% (Nagelkerke R^2) of the variance in AKI and correctly classified (Percentage accuracy in classification) 95.7% of cases, with PPV 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 to 1.083. Increasing CPK, age, use of psychotropic drugs, and male gender insignificantly increased the likelihood of exhibiting AKI.

DISCUSSION

The most serious complication of rhabdomyolysis 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 rhabdomyolysis [9].

In one study by Mousavi, the prevalence of AKI was 15% of 114 patients acutely intoxicated with rhabdomyolysis, which is compatible with our results [10]. The prevalence of AKI in acute intoxicated with rhabdomyolysis was 37,1% in the retrospective study by Rogliano [11]. In patients with rhabdomyolysis 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 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 rhabdomyolysis 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 group of authors AKI is associated with a higher rate of opioid and cocaine use in patients with rhabdomyolysis [13]. Rogliano and autors reported that, overdoses with beta-blockers, calcium-channel inhibitors, acetaminophen, colchicine, lithium, angiotensin-converting enzyme (ACE) and inhibitors/angiotensin II-receptor-blockers were significantly associated with an increased risk of AKI in poisoned patients with rhabdomyolysis [11].

Rhabdomyolysis is not the only cause of AKI in acutely intoxicated patients, unlike rhabdomyolysis resulting from trauma. According to our analysis, patients intoxicated with chemicals who developed AKI were in the group with mild to moderate rhabdomyolysis 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 rhabdomyolysis [14]. Coma, shock, hemolysis, and anuric kidney injury has been reported with poisoning with acetic acid [15].

The results indicate that certain toxic agents in acutely intoxicated patients with rhabdomyolysis may play an important role in the development of AKI. We found that patients with AKI acutely intoxicated with rhabdomyolysis as well as those intoxicated with psychotropic substances had significantly higher values for creatine, BUN, 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 and co-workers, for a significant positive correlation between serum creatinine values and CK values [10]. Regarding the increased risk of developing complications such as AKI, similar findings were found in the study by Pajoumond and authors [16]. Eizadi-Mood and co-workers in the prospective study indicated

that a CK value> 10000 IU / L was associated with a higher complication rate and could be an acceptable predictor of outcome in intoxicated patients [17]. In one retrospective study by Nilsen, in patients with rhabdomyolysis, elevated initial CK values were associated with an increased risk of AKI [18]. 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. serum creatinine ≥ 125 μmol/L on admission was the highest predictive variable for AKI in poisonings [11].

Recommendations to lower the risk of AKI in patients with rhabdomyolysis include fluids to correct hypovolemia, achieve adequate diuresis with a goal urine output of 300mL/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 renal replacement therapy (RRT) in our analysis in patients acutely intoxicated with rhabdomyolysis is 9.3%. Intermittent RRT was used in our patients with rhabdomyolysis due to acute intoxication with psychotropic and chemical substances. RTT was initiated 2 or 3 days after admission and our patients required one hemodialysis session.

According to the literature, the need for RRT in patients with rhabdomyolysis ranges from 4-20% [20]. The prevalence of RRT is significantly higher in psychotropic compared to chemical intoxications. In acutely intoxicated patients with rhabdomyolysis 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 in his study reported that in acutely intoxicated patients with coma increased CK values were associated with an increased need for dialysis [17]. According to a study by Dadpour, approximately 80% of patients with serum CK levels <10000 IU / L required dialysis [21]. In contrast to our results, the study by Pajoumand and co-workers, presents that there is no significant correlation between CK levels and the need for dialysis [16]. Stopping RRT depends on multiples factors: resolution of the underlying cause, creatine level and able to be managed effectively using other therapies (e.g. furosemide for fluid balance) [22]. In most patients with rhabdomyolysis, renal function is restored within a few months [23, 24].

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

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REFERENCES

1. Samuel HU, Balasubramaniyan T, Thirumavalavan S, Vasudevan C, Senthil Kumar RP, Murugesan V, Abraham A. Rhabdomyolysis with myoglobin-induced acute kidney injury: A case series of four cases. Indian J Pathol Microbiol. 2021 Apr-Jun;64(2):382-384. doi: 10.4103/IJPM.IJPM_89_20. PMID: 33851641.
2. Long B, Koyfman A, Gottlieb M. An evidence-based narrative review of the emergency department evaluation and management of rhabdomyolysis. Am J Emerg Med. 2019;37(3):518-523. doi: 10.1016/j.ajem.2018.12.061. Epub 2019 Jan 2. PMID: 30630682.
3. Ahmad S, Anees M, Elahi I, Fazal-E-Mateen. Rhabdomyolysis Leading to Acute Kidney Injury. J Coll Physicians Surg Pak. 2021 Feb;31(2):235-237. doi: 10.29271/jcpsp.2021.02.235. PMID: 33645199.
4. Somagutta MR, Pagad S, Sridharan S, Nanthakumaran S, Arnold AA, May V et.al. Role of Bicarbonates and Mannitol in Rhabdomyolysis: A Comprehensive Review. Cureus. 2020 Aug 14;12(8):e9742. doi: 10.7759/cureus.9742. PMID: 32944457.
5. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009 Jul 2;361(1):62-72. doi: 10.1056/NEJMra0801327. Erratum in: N Engl J Med. 2011 May 19;364(20):1982. doi: 10.1056/NEJMra0801327. PMID: 19571284.
6. Yang J, Zhou J, Wang X, Wang S, Tang Y, Yang L. Risk factors for severe acute kidney injury among patients with rhabdomyolysis. BMC Nephrol. 2020 Nov 23;21(1):498. doi: 10.1186/s12882-020-02104-0. PMID: 33225908.
7. Weidhase L, de Fallois J, Haußig E, Kaiser T, Mende M, Petros S. Myoglobin clearance with continuous veno-venous hemodialysis using high cutoff dialyzer versus continuous veno-venous hemodiafiltration using high-flux dialyzer: a prospective randomized controlled trial. Crit Care. 2020 Nov 11;24(1):644. doi: 10.1186/s13054-020-03366-8. PMID: 33176824.
8. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013 Feb 4;17(1):204. doi: 10.1186/cc11454. PMID: 23394211.
9. Stanley M, Chippa V, Aeddula NR, Quintanilla Rodriguez BS, Adigun R. Rhabdomyolysis. 2023 Apr 16. PMID: 28846335.
10. Mousavi SR, Vahabzadeh M, Mahdizadeh A, Vafaee M, Sadeghi M, Afshari R, et.al. Rhabdomyolysis in 114 patients with acute poisonings. J Res Med Sci. 2015 Mar;20(3):239-43. PMID: 26109969.
11. Rogliano PF, Voicu S, Labat L, Deye N, Malissin I, Laplanche JL, et al. Acute Poisoning with Rhabdomyolysis in the Intensive Care Unit: Risk Factors for Acute Kidney Injury and Renal Replacement Therapy Requirement. Toxics. 2020 Sep 28;8(4):79. doi: 10.3390/toxics8040079. PMID: 32998294.
12. Janković SR, Stosić JJ, Vucinić S, Vukcević NP, Ercegović GV. Causes of rhabdomyolysis in acute poisonings. Vojnosanit Pregl. 2013; 70:1039-45. doi: 10.2298/vsp1311039j. PMID: 24397200.
13. Yang CW, Li S, Dong Y, Paliwal N, Wang Y. Epidemiology and the Impact of Acute Kidney Injury on Outcomes in Patients with Rhabdomyolysis. J Clin Med. 2021 May 1;10(9):1950. doi: 10.3390/jcm10091950. PMID: 34062839.
14. Lee FY, Chen WK, Lin CL, Lai CY, Wu YS, Lin IC, et al. Organophosphate Poisoning and Subsequent Acute Kidney Injury Risk: A Nationwide Population-Based Cohort Study. Medicine (Baltimore). 2015 Nov;94(47):e2107. doi: 10.1097/MD.0000000000002107. PMID: 26632728.
15. Brusin KM, Krayeva YV. Acetic Acid Poisoning: 400 Cases Reviewed. APJM of Med Toxicol. 2012; 1:1-7. doi:10.22038/APJMT.2012.19.
16. Pajoum A, Fahim F, Akhlaghdoust M, Zamani N, Amirfirooz Z, Dehdehasti M. Rhabdomyolysis and Acute Poisoning; a Brief Report. Emerg (Tehran). 2018;6(1):e56. PMID: 30584572.

17. Eizadi-Mood N, Sabzghabaee AM, Gheshlaghi F, Mehrzad F, Fallah Z. Admission creatine phosphokinase in acute poisoning: is it a predictive factor for the treatment outcome? J Pak Med Assoc. 2012; 62:67-70. PMID: 22768464.

18. Nielsen FE, Cordtz JJ, Rasmussen TB, Christiansen CF. The Association Between Rhabdomyolysis, Acute Kidney Injury, Renal Replacement Therapy, and Mortality. Clin Epidemiol. 2020 Sep 24;12:989-995. doi: 10.2147/CLEP.S254516. PMID: 33061646.

19. Tarazona V, Figueiredo S, Hamada S, Pochard J, Haines RW, Prowle JR, et.al. Admission serum myoglobin and the development of acute kidney injury after major trauma. Ann Intensive Care. 2021 Sep 24;11(1):140. doi: 10.1186/s13613-021-00924-3. PMID: 34559325.

20. Vangstad M, Bjornaas MA, Jacobsen D. Rhabdomyolysis: a 10-year retrospective study of patients treated in a medical department. Eur J Emerg Med. 2019;26:199-204. doi: 10.1097/MEJ.0000000000000510. PMID: 29068810.

21. Dadpour B, Tajoddini S, ShaarbafEidgahi E, Shokouhizadeh M, Shafahi A. Role of Serum Creatinine Phosphokinase in Outcome Prediction of Intoxicated Patients; a Brief Report. Emerg (Tehran). 2017;5(1): e63. PMID: 28894778.

22. Mishra RC, Sodhi K, Prakash KC, Tyagi N, Chanchalani G, Annigeri RA et al. ISCCM Guidelines on Acute Kidney Injury and Renal Replacement Therapy. Indian J Crit Care Med. 2022 Oct;26(Suppl 2):S13-S42. doi: 10.5005/jp-journals-10071-24109. PMID: 36896356.

23. Subashri M, Sujit S, Thirumalvalavan K, Poongodi A, Srinivasaprasad ND, Edwin Fernando M. Rhabdomyolysis-associated Acute Kidney Injury. Indian J Nephrol. 2023 Mar-Apr;33(2):114-118. doi: 10.4103/ijn.ijn_247_21. Epub 2023 Feb 20. PMID: 37234438.

24. Lim AKH, Azraai M, Pham JH, Looi WF, Bennett C. The Association Between Illicit Drug Use and the Duration of Renal Replacement Therapy in Patients With Acute Kidney Injury From Severe Rhabdomyolysis. Front Med (Lausanne). 2020 Nov 9;7:588114. doi: 10.3389/fmed.2020.588114. PMID: 33240909.

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	$\bar{X}$ ± SD	39.93 ± 13.41
	Min/Max	26/53
	Median (IQR)	40 (36–47)
Chemical	$\bar{X}$ ± 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

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; p > 0.001*
		yes	14	18.1	10.4	9.9	14.1	25.3	
	Chemical								
	AKI	no	37	5.9	2.5	4.1	5.4	6.8	Z = - 2.087; p = 0.037*
		yes	7	10.3	5.9	5.9	7.3	16.1	
	Total								
	AKI	no	119	5.2	2.9	3.5	4.7	5.8	Z = -5.906; p > 0.01*
		yes	21	15.5	9.7	7	12.6	22.7	
Creatinine	psychoactive								
	AKI	no	82	81	18.9	65.8	78	91.6	Z = -5.949; p > 0.001*
		yes	14	332.7	255.4	209.8	277.1	359.3	
	chemical								
	AKI	no	37	86.9	23.4	73.8	83	105.1	Z = -2.070; p = 0.038*
		yes	7	170.6	103.7	69	145.8	279	
	Total								
	AKI	no	119	82.8	20.5	67	79	96	Z = -6.143; p > 0.01*
		yes	21	278.6	227.5	143.4	272.9	333.9	
Na	Psychoactive								
	AKI	no	82	137.5	4.3	136	138	139.6	Z = -2.915; p = 0.004*
		yes	14	131.1	7.6	125	131.5	139	
	Chemical								
	AKI	no	37	137.8	3.5	136	137	140.1	z = -1.012; p = 0311
		yes	7	141.6	8.5	134.6	140	144	
	Total								
	AKI	no	119	137.6	4.1	136	138	139.8	Z = -1.699; p = 0.89
		yes	21	134.6	9.2	129	134.6	139.6	
K	Psychoactive								
	AKI	no	82	4	0.7	3.6	3.9	4.5	Z = - 3.630; p > 0.001*
		yes	14	5.4	1.2	4.5	6	6.3	
	Chemical								
	AKI	no	37	4.5	1	3.9	4.1	4.7	Z = -1.220; p = 0.22
		yes	7	4.5	0.8	4.2	4.7	5.1	
	Total								
	AKI	no	119	4.2	0.8	3.7	4	4.6	Z = -3.588;p > 0.01*
		yes	21	5.1	1.1	4.2	5	6.1	
Ca	Psychoactive								
	AKI	no	82	2.3	0.3	2.2	2.2	2.4	Z = - 2.760; p = 0.006*
		yes	14	2.1	0.2	2	2.1	2.2	
	Chemical								
	AKI	no	37	2.32	0.27	2.150	2.400	2.485	Z = -1.141; P = 0.25
		yes	7	2.26	0.17	2.100	2.290	2.390	
	Total								
	AKI	no	119	2.3	0.3	2.2	2.3	2.4	Z = 4.277; P = 0.008*
		yes	21	2.1	0.2	2.1	2.1	2.3	
AST	Psychoactive								
	AKI	no	82	76.9	140.5	24	36.5	59.3	Z = 5.6576; p = 0.00001*
		yes	14	990.9	669.2	733	822	1171	
	Chemical								
	AKI	no	37	81.9	161.3	25.5	34	64.1	Z = 0.9787; p = 0.3277
		yes	7	344.5	556.8	29	38.7	804.6	
	Total								

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

AKI – acute kidney injury; AST – aspartate aminotransferase; ALT – alanine aminotransferase; CK – creatine kinase; hs-troponin I – high-sensitivity troponin I;

Mann–Whitney U test = Z;

*significant for $p < 0.05$

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	$\bar{X}$ ± 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	$\bar{X}$ ± 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	$\bar{X}$ ± 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	$\bar{X}$ ± 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	$\bar{X}$ ± 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	$\bar{X}$ ± 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	$\bar{X}$ ± 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	$\bar{X}$ ± 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	$\bar{X}$ ± 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 $p < 0.05$

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	-2.0*
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

