ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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# Detection of Rhabdomyolysis in Patients Admitted to Emergency Department due to Drug Overdose as a Suicide Attempt: A Propective Original Clinical Study

## İntihar Amaçlı İlaç Alımı Nedeni ile Acil Servise Başvuran Hastalarda Rabdomiyolizin Araştırılması: Prospektif Orijinal Klinik Çalışma

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**ABSTRACT Objective:** Drug-induced rhabdomyolysis is the most common cause of disorders leading to acquired muscular inflammation. The aim of this study is to investigate rhabdomyolysis frequency in patients admitted to the emergency room (ER) due to one or different types of multiple drug ingestion with suicidal intentions. **Material and Methods:** This prospective clinical study was performed between June 2013 and November 2013 in Dr. Lütfi Kırdar Kartal Training and Research Hospital's ER, which had a daily admittance average of 800-1000 patients. The study included 103 patients. Creatinephosphokinase in the blood and myoglobin in the urine examined at the 3rd, 6th, 12th and 24th hours of admission to the ER. **Results:** Of the patients, 77 (74.8%) were female and 26 (25.2%) were male. Mean age was 28.8±9.5 years. Male subjects ingested a greater variety and a greater number of drugs than female subjects ($p<0.05$). Creatine phosphokinase level was found to be higher in the patients who took a higher number of drugs. Creatine phosphokinase was higher than 171 (U/L) in 15 patients (14.6%). Myoglobinuria was detected in 7.8% of all patients. No rhabdomyolysis was observed in patients who were admitted to the hospital within the first 3 hours of ingestion. The most commonly used agent for suicide attempt was non-steroidal anti-inflammatory drugs (NSAIDs) (36.9%), paracetamol (31.1%) and antidepressants (30.1%). **Conclusion:** It was found that patients with delayed admission to the ER had a higher incidence of rhabdomyolysis. Antidepressants were the third leading agents used for suicidal intentions following NSAIDs and paracetamol.

**Keywords:** Rhabdomyolysis; suicide attempt

**ÖZET Amaç:** İlaçların tetiklediği rabdomiyoliz kazanılmış kas inflamasyonu nedenlerinden en sık olanıdır. Bu çalışmanın amacı öz kıyım amaçlı bir veya farklı türde çok miktarda ilaç alımı nedeni ile acil servise kabul edilen hastalarda rabdomiyoliz sıklığını araştırmaktır. **Gereç ve Yöntemler:** Bu prospektif klinik çalışma günlük ortalama 800-1000 hastanın başvurduğu Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi Acil servisinde 2013 yılı Haziran ve Kasım ayları arasında yapıldı. Çalışmaya 103 hasta dahil edildi. Hastaların acil servise kabulünden sonra 3'üncü, 6'ıncı, 12'inci ve 24'üncü saatlerde kan kreatin fosfokinaz ve idrarda miyoglobin değerlerine bakıldı. **Bulgular:** Hastaların 77'si (%74,8) kadın ve 26'sı (%25,2) erkekti. Yaş ortalamaları 28,8±9,5 yıldı. Erkek hastalar kadın hastalardan daha fazla miktarda ve çeşitte ilaç almışlardı ($p<0,05$). Yüksek sayıda ilaç alan hastalarda kreatin fosfokinaz seviyesi yüksek bulundu. Kreatin fosfokinaz 15 hastada (%14,6) 171(U/L) den daha yüksekti. Miyoglobinüri hastaların %7.8'inde tespit edildi. İlaç alımının ilk üç saati içinde acil servise başvuran hastaların hiçbirinde rabdomiyoliz görülmedi. Öz kıyım amaçlı en sık kullanılan ajanlar non-steroid antiinflamatuar ilaçlar (NSAİİ) (%36,9), parasetamol (%31,1) ve antidepresanlardı (%30,1). **Sonuç:** Gecikmeli olarak acil servise getirilen hastalarda rabdomiyoliz insidansının daha yüksek olduğu tespit edildi. Öz kıyım amaçlı olarak NSAİİ ve parasetamolü takiben antidepresanlar üçüncü sıklıkta kullanılan ilaçlardı.

**Anahtar Kelimeler:** Rabdomiyoliz; intihar girişimi

Rhabdomyolysis, due to the destruction of the muscle cells, is a severe syndrome that can cause life-threatening electrolyte disorders and renal insufficiency, manifested with increased lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and myoglobin levels in plasma.[1] Rhabdomyolysis may include a wide spectrum of symptoms ranging from

non-specific findings such as fatigue and myalgia to acute renal failure. Additionally, almost half of the patients with rhabdomyolysis have a classical triad including muscle pain, weakness and dark urine.[2]

Rhabdomyolysis can result from acquired and inherited causes. The acquired causes constitute 75% of all the cases.[3] While alcohol/drug abuse, medications, toxic agents, infections, endocrine disorders, muscle ischemia, idiopathic inflammatory rhabdomyolysis, extreme physical exertion are the nontraumatic acquired causes of rhabdomyolysis; multiple injuries, crush injury, high-voltage electrical injury, extensive burns, vascular/orthopedic surgery, and prolonged immobility are traumatic causes of rhabdomyolysis.[4] Substance abuse and medication-induced rhabdomyolysis (34%-11%) are the most common causes of disorders leading to muscular inflammation.[5] Concomitant and increased number of drug use significantly increases the risk of rhabdomyolysis.[6]

The aim of this study is to investigate rhabdomyolysis frequency in patients admitted to the emergency department due to drug overdose with suicidal intentions and to identify patients with high risk of rhabdomyolysis.

## MATERIAL AND METHODS

This prospective clinical study was performed between June 2013 and November 2013 in Dr. Lütfi Kirdar Kartal Training and Research Hospital's emergency room, which had a daily admittance average of 800-1000 patients. The ethical approval (11/06/2013 No: 89513307/163) of the study was obtained from the Ethics Committee of Dr. Lütfi Kirdar Kartal Training and Research Hospital.

*Study Group:*

Exclusion Criteria:

- Patients in need of intensive care,

- Patients under 16 years of age,

- Patients with an underlying disease that may cause rhabdomyolysis,

- Patients with a history of excessive exercise prior to admission,

- Patients with recent infections,

- Patients with a recent history of crush injuries,

- Patients who experience seizures,

- Patients who have taken the medication more than 24 hours ago,

- Patients who do not want to participate in the study.

- Patients who had aggression and agitation.

Inclusion Criteria:

- Patients older than 16,

- Patients admitted to the emergency department within the first 24 hours of drug intake,

- Patients who agreed to participate in the study.

Informed consent was obtained from all patients in the study. Sociodemographic and clinical data collection form was filled out for all patients.

The patients who were admitted to the hospital within one hour after the drug ingestion were given gastric lavage. Gastric lavage was not routinely used for poisoned patients. It was performed to the patients admitted within 60 minutes of overdose and only with drugs not absorbed by charcoal. Antidotes were given to patients with antidote therapy indications. All the patients were hydrated properly with 100 cc/hour 0.9% saline.

The patients were observed in the emergency department for 24 hours, and CPK in the blood sample and myoglobin in the urine sample were studied at the 3$^{rd}$, 6$^{th}$, 12$^{th}$ and 24$^{th}$ hours after the patients were admitted to the emergency department. The peak time of CPK and presence or absence of myoglobinuria were also recorded. Rhabdomyolysis was diagnosed in the patients with myoglobin from their urine samples or in those who had five times higher CPK than the upper limit of normal range (171 U/L).

### SOCIODEMOGRAPHIC AND CLINICAL DATA COLLECTION FORM

This form was completed by researchers based on the answers of the participants. The form included

questions regarding age, sex, marital status, smoking habit, alcohol consumption, and active substance of drugs ingested for suicidal intentions, the admission time of the patients after drug overdose, CPK, presence or absence of myoglobin in urine, peak time of CPK, employed therapeutic interventions (hydration, antidote, gastric lavage, and active charcoal) and history of previous diseases or medications.

### STATISTICAL ANALYSIS

All data were analyzed with SPSS for Windows version 22.0. Descriptive statistics were summarized as mean, standard deviation, median, minimum and maximum values, and the frequency distributions. Kolmogorov-Smirnov test was used to test if a variable follows a given distribution. To compare differences between two groups when the dependent variable is continuous we employed the Mann Whitney U test while we used the Chi-square test to assess if two categorical variables are independent. The estimated 95% of confidence interval is provided and value of $p<0.05$ was accepted statistically significant.

## RESULTS

The study included 103 patients older than 16 years who were admitted to the emergency department with one or different types of multiple drugs overdose with suicidal intentions. There were 77 (74.8%) female and 26 (25.2%) male subjects in the study. Mean age was 28.8±9.5 years. The mean number of drug overdose was 26.0±18.5. The number of the patients who ingested multiple tablets of the same type of drug was 45 (43.7%), while the number of those who ingested multiple tablets of different types was 58 (56.3%). The most commonly used agent for suicide attempt was non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. as diclofenac, aspirin, ibuprofen, ketoprofen, naproxen and etodolac) appearing in 38 (36.9%) patients, which was followed by paracetamol in 32 (31.1%) patients and antidepressants in 31 (30.1%). In 98.1% of all patients received therapeutic interventions, including hydration for 99 (96.1%) patients, active charcoal administration for 68 (66.0%) patients, gastric lavage for 58 (56.3%) patients and antidote administration (N-acetylcysteine for paracetamol intoxication) for 12 (11.7%) patients (the antidote was not used in all patients, we only used it for patients we could supply). Mean CPK was 129.6±142.3 U/L and mean peak time of CPK was 4.8±3.5 hours (Table 1). CPK was higher than 171U/L in 15 patients (14.6%). It was found that 8 (7.8%) patients developed myoglobinuria.

There was a statistically significant relationship between myoglobinuria and the number of the drugs ($p=0.002$). A statistically significant association between myoglobinuria and CPK level ($p<0.001$) was also observed. In addition, the admission time of the patients was positively correlated with CPK level or peak time of CPK ($p=0.001$).

The rate of drug overdose due to different types of drug was found to be significantly higher in male (76.9%) than in female (49.4%) subjects ($p=0.014$). When the rates of antibiotics, paracetamol, antidepressant agents, H2 receptor blockers, muscular relaxants, cardiac agents, oral antiglycemic agents, and miscellaneous or unknown drug usage, were compared there was no significant difference between male and female subjects ($p>0.05$). However, the rate of NSAID use was significantly higher in male than in female patients ($p=0.011$). The mean number of drug overdose was 32.0±22.9 in male and 23.9±16.05 in female subjects, indicating a significantly higher number of drug overdose for the male subjects ($p=0.024$).

The mean number of drug overdose was 30.1±18.9 in the patients who took multiple tablets of different drugs and 20.6±16.7 for the patients who used multiple tablets of the same type of drug. There was a significant difference in the number of drugs ingested among the patients consuming multiple tablets of different drugs and those using multiple tablets of the same drug ($p<0.001$). However, there were no significant differences among the patients in their admission time to the emergency department, CPK and their peak times ($p>0.05$) (Table 2).

**TABLE 1:** Sociodemographic characteristics and values of the patients.

| | N (%) | (Mean ± SD) |
|---|---|---|
| **Age (year)** | | 28.8±9.5 |
| **Gender** | | |
| Female | 77 (74.8) | |
| Male | 26 (25.2) | |
| **Number of drug** | | 26.0±18.5 |
| **Admission time of patients** | | 2.7±3.1 |
| **Drug overdose** | | |
| Same type of drug | 45 (43.7) | |
| Different types of drugs | 58 (56.3) | |
| **Drug** | | |
| Antibiotics | 24 (23.3) | |
| Paracetamol | 32 (31.1) | |
| NSAIDs | 38 (36.9) | |
| Antidepressants | 31 (30.1) | |
| H2 receptor blockers | 8 (7.8) | |
| Muscle relaxants | 17 (16.5) | |
| Cardiac drugs | 8 (7.8) | |
| Oral antidiabetics | 1(1.0) | |
| Others | 20 (19.4) | |
| Unknown | 9 (8.7) | |
| **Treatment** | | |
| Hydration | 99 (96.1) | |
| Gastric lavage | 58 (56.3) | |
| Activated carbon | 68 (66.0) | |
| Antidote | 12 (11.7) | |
| **Myoglobinuria** | 8 (7.8) | |
| **CPK (U/L)** | | 129±142.3 |
| **Number of the patients according to CPK level** | | |
| <171 (U/L) | 88 (85.4) | |
| >171 (U/L) | 15 (14.6) | |
| **Mean peak time of CPK(hour)** | | 4.8±3.5 |

**NSAIDs:** Non-steroidal anti-inflammatory drugs; **CPK:** Creatine phosphokinase; **SD:** Standard deviation.

The mean number of drug overdose was 45.5±23.5 in the patients with myoglobinuria and 24.6±17.2 in the patients without myoglobinuria (p=0.002). Mean admission time of the patients with myoglobinuria was 5.5±2.1 and their peak time of CPK was 7.1±3.2 hours. However, mean admission time of patients without myoglobinuria was 3.0±2.5 and their peak time of CPK was 4.6±3.5 hours (p<0.001). Mean CPK 519±285.7 U/L in the patients with myoglobinuria and was 96.8±43.2 U/L in those without myoglobinuria (p<0.001). The number of drug overdose, the admission time of patients, CPK level, and the peak time of CPK were significantly higher those with myoglobinuria than in the patients without myoglobinuria (p=0.001) (Table 3).

## DISCUSSION

Up to the date, the frequency of rhabdomyolysis has been well investigated however, researches on the frequency of rhabdomyolysis due to drug over dose as a suicide attempt are relatively limited.

**TABLE 2:** The comparison of clinical values between male and female patients.

| | Female N (%) | Male N (%) | p |
|---|---|---|---|
| **Drug overdose** | | | |
| Same type of drug | 39 (50.6) | 6 (23.1) | 0.014 |
| Different types of drugs | 38 (49.4) | 20 (76.9) | |
| **Drug** | | | |
| Antibiotics | 19 (24.7) | 5 (19.2) | |
| Paracetamol | 21 (27.3) | 11 (42.3) | |
| NSAIDs | 23 (29.9) | 15 (57.7) | |
| Antidepressants | 24 (31.2) | 7 (26.9) | |
| H2 receptor blockers | 6 (7.8) | 2 (7.7) | |
| Muscle relaxants | 11 (14.3) | 6 (23.1) | |
| Cardiac drugs | 4 (5.2) | 4 (15.4) | |
| Oral antidiabetics | 1 (1.3) | 0 (0.0) | |
| Others | 16 (20.8) | 4 (15.4) | |
| Unknown | 6 (7.8) | 3 (11.5) | |
| **Number of drugs** (Mean±SD) | 23.9±16.5 | 32.0±22.9 | **0.024** |
| **Admission time** (Mean±SD) | 2.6±2.2 | 3.1±4.8 | 0.693 |
| **CPK** (U/L) (Mean±SD) | 131.2±159.0 | 124.8±75.5 | 0.068 |
| **Peak time of CPK** (Mean±SD) | 4.6±3.0 | 5.2±4.8 | 0.911 |

**NSAIDs:** Non-steroidal anti-inflammatory drugs; **CPK:** Creatine phosphokinase.

**TABLE 3:** The comparison of clinical values between male and female patients.

| | Myoglobinuria(-) | Myoglobinuria(+) | p |
|---|---|---|---|
| Number of drugs (Mean+SD) | 24.3±17.2 | 45.5±23.5 | **0.002*** |
| Admission time (Mean+SD) | 3.0±2.5 | 5.5±2.1 | **0.000*** |
| CPK (Mean+SD) | 96.8±43.2 | 519.4±285.7 | **0.000*** |
| Peak time of CPK (Mean+SD) | 4.6±3.5 | 7.1±3.2 | **0.001*** |

**SD:** Standard deviation; **CPK:** Creatine phosphokinase.

Drug-induced rhabdomyolysis can occur due to several agents that are used for therapeutic purposes as well as multiple drug overdose with suicidal intentions. These agents can cause neuromuscular junction disorders, muscle pain, and myotonia in addition to CPK elevation. Thus, the conditions of suicidal patients with multiple medication intake or patients using drugs that can cause rhabdomyolysis should be evaluated in terms of rhabdomyolysis.[7] In our study, rhabdomyolysis was detected in 7.8% of all the patients who attempted to commit suicide by multiple drug overdose. In a previous survey of 181 patients with suspected rhabdomyolysis after presenting to the hospital for poisoning, the patients with CPK >975 U/L were considered to have rhabdomyolysis. 76% of these patients had CPK 975 U/L. It was seen that rhabdomyolysis developed after multiple drug overdose in 6% of the cases.[1] In another study, which included 103 patients with intoxication due to drug overdose, rhabdomyolysis was detected in 7% of the patients with CPK >1000 U/L. The clinical findings of rhabdomyolysis were observed in 2 patients, one with salicylate intoxication and the other with heroin intoxication.[8] Wongrakpanich et al., explained in their study for patients over 65 years old that, the prevalence of rhabdomyolysis due to statins and other drugs was found to be 2.4% and 1.8% respectively.[9] Black et al. reported the prevalence of rhabdomyolysis as 1% in patients aged 20-75 years; and of this rhabdomyolysis 28% was related to drug overdose and 20% was due to sep-

ticemia.[10] In another study, 24% of the patients presenting to the emergency department due to cocaine use have been shown to develop rhabdomyolysis.[11]

In our study, all patients who were admitted to the emergency department after 5.5 hours were detected to develop rhabdomyolysis. We observed that all patients who presented before 5.5 hours had no rhabdomyolysis. We considered that early treatment including gastric lavage, activated charcoal was effective in the patients who admitted to the emergency department shortly after overdose. A recent study has shown that when activated charcoal is given shortly after overdose, systemic drug absorption is significantly reduced.[12] It is suggested that the patients admitted to emergency department due to drug overdose may not need to be followed up for rhabdomyolysis if the patients were received medications to prevent drug absorption from the intestine shortly after overdose.

Drug-induced rhabdomyolysis can occur from a variety of different mechanisms and types of muscle injury like necrosis, vascular changes, or mitochondrial dysfunction.[13] Plasma CPK begins to rise in 2 to 12 hours after the muscle destruction, and peak values for CPK are observed at any time between 1 and 3 days.[14,15] However, in our study, the peak time of CPK in the patients with rhabdomyolysis ranged from 12.6 to 17.9 hours. Our results are different from the literature in the sense that the simultaneous intake of multiple drugs with different contents may cause rhabdomyolysis earlier by acting through different mechanisms. In addition, early initiation of hydration as a routine treatment protocol in the patients presented with drug use with suicidal intentions may result in premature termination of the CPK peak.

Rhabdomyolysis may not develop in the acute phase. Patients with drug overdose with suicidal intentions tend to have rhabdomyolysis in their follow-ups. For this reason, a long-term monitoring of such patients is recommended.

Many medications can cause rhabdomyolysis. The most common substances inducing rhabdomyolysis are corticosteroids, lipid-lowering drug, propoxyphene, neuroleptics, zidovudine, chloroquine, phenytoin, aminocaproic acid, and azathioprine.[16,17] In our study, it was seen that CPK elevation was more familiar with NSAIDs and paracetamol which are frequently used and readily available, and antidepressants which have been prescribed more commonly in the recent years.

In our study, the most commonly used drugs for suicidal intentions were NSAIDs followed by paracetamols.

Non-steroidal anti-inflammatory drugs and paracetamols are over-the-counter drugs that can be purchased easily. Thus, availability makes it also easy to use them for suicidal purposes. Antidepressants were the third leading agents used for suicide attempts. Patients who take antidepressants often require long-term treatment and, in some countries, patients might be prescribed with multiple boxes of drugs for the next follow-ups to come in a few months. This may incite already suicidal patients who have had multiple doses of these drugs to commit suicide at once because of this availability. To prevent this, it may be the right method for these patients at risk of suicide to obtain only a limited number of drugs.

In a study in which sociodemographic characteristics, it was reported that the average age was 33.6±12.3 years in the cases who admitted to the emergency department with a suicide attempt.[18] In our study, the mean age was 28.8±9.5 years, consistently with the study mentioned above. The female/male ratio was reported to be 0.58 in cases who were presented to the emergency department with a suicide attempt in a survey from China while suicide prevalence was found as 79:100.000 with a female/male ratio of 3 in a study from Thailand.[19,20] In our study, the incidence of suicide was higher in female than in male subjects, but the number and types of drugs ingested were found to be higher in male than in female subjects. This shows that male subjects are using more efficient methods for suicide attempts and have a higher risk of severe complications such as rhabdomyolysis. Rajapakse's study showed that males had significantly higher levels of suicidal intent when compared to females.[21]

## LIMITATIONS

This study has some limitations. First is the limited number of the patients. Secondly, the patients were observed for only 24 hours because it was a crowded emergency service and the number of beds for monitoring was inadequate. Intensive care patients were also not included in the study. Finally, we did not measure LDH level of the patients and did not include data from physical and psychological findings in the analysis.

## CONCLUSION

In our study, it was found that different types and amounts of drugs ingested were significantly higher in male than in female subjects. Higher CPK levels were found in patients with a higher number of drug overdose. Therefore, the number of ingested drugs might be a risk factor for rhabdomyolysis occurrence. It was found that the number of drugs taken, admission time to the emergency department, CPK level and its peak time were the factors affecting rhabdomyolysis development. It was also found that patients with delayed admission time had a higher incidence of rhabdomyolysis, which clearly showed us the importance of early intervention.

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### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

***Idea/Concept:*** *Hilal Hocagil, Abdullah Cüneyt Hocagil;* ***Design:*** *Hilal Hocagil, Mehmet Tatlı;* ***Control/Supervision:*** *Hilal Hocagil, Tugba Akkaya Hocagil, Filiz İzci;* ***Data Collection and/or Processing:*** *Hilal Hocagil, Mehmet Tatlı, Semih Sözen;* ***Analysis and/or Interpretation:*** *Tugba Akkaya Hocagil, Hilal Hocagil;* ***Literature Review:*** *Hilal Hocagil, Filiz İzci, Abdullah Cüneyt Hocagil, Semih Sözen;* ***Writing the Article:*** *Hilal Hocagil, Filiz İzci;* ***Critical Review:*** *Abdullah Cüneyt Hocagil, Mehmet Tatlı;* ***References and Fundings:*** *Hilal Hocagil, Mehmet Tatlı, Semih Sözen.*

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