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What About Cardiotoxicity? An Evaluation of Cardiac Markers in Children with Suicidal Attempt by Drug Overdose

Peki ya Kardiyotoksisite? Aşırı Doz İlaç Alımı ile İntihar Girişiminde Bulunan Çocuklarda, Kardiyak Belirteçlerin Değerlendirilmesi

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ABSTRACT Objective: Overdose drug intake is a common method of suicide attempt among children and adolescents which can cause cardiac complications. However, the current body of knowledge about cardiotoxicity largely consists of limited adult studies and case reports. We investigated the prevalence of cardiac involvement through cardiac biomarkers and electrocardiographic findings of suicidal attempt at pediatric age. **Material and Methods:** A retrospective review of 158 suicide attempts by drug overdose under age of 18 who were admitted to pediatric emergency department was made. Demographic features, applied medical procedures, patients' routine laboratory findings, electrocardiographic findings and serum levels of high sensitive troponin I, CK-MB and myoblobin were rewieved. **Results:** Of these 158 cases, 82.3% (130) were girls and the average age was 15.5±1.4 (7-17) years. Seventy nine cases (50%) were multidrug intake. The mean duration of admission to the emergency room was 3.9 hours after drug intake. None of the cases had obvious electrocardiographic changes in terms of myocardial injury. However, mild QRS widening and QT prolongation were detected in three patients. Elevated myoglobin level was detected in 36 cases whereas two cases had elevated CK-MB levels. Increased level of high sensitive troponin I level was in only one case who took overdose asetil salisylic acide and mianserine. **Conclusion:** Cardiac complications may occur in suicidal attempt by drug overdose in children. High clinical suspicion with evaluation through electrocardiography and cardiac biomarkers is needed to detect this vital condition.

Keywords: Cardiotoxicity; drug overdose; pediatric age; suicide

ÖZET Amaç: Aşırı dozda ilaç alımı, çocuk ve ergenlerde kardiyak komplikasyonlara neden olabilen yaygın bir intihar girişimi yöntemidir. Bununla birlikte, kardiyotoksisite hakkında mevcut bilgi birikimi büyük ölçüde sınırlı yetişkin çalışmaları ve vaka raporlarından oluşmaktadır. Bu çalışmada , intihar girişimi bulunan çocuklarda kardiyak etkilenimi, kardiyak biyobelirteçler ve elektrokardiyografik bulgular ile değerlendirdik. **Gereç ve Yöntemler:** Çocuk acil servisine intihar amaçlı aşırı dozda ilaç alımı ile başvuran 18 yaş altı 158 hasta retrospektif olarak gözden geçirildi. Demografik özellikler, uygulanan tıbbi prosedürler, hastaların rutin laboratuvar bulguları, elektrokardiyografik bulguları ve yüksek duyarlı troponin I, CK-MB ve miyoblobin düzeyleri değerlendirildi. **Bulgular:** Çalışmaya dahil olan 158 vakanın 130'u (%82,3) kız, yaş ortalaması 15,5±1,4 (7-17) yıl idi. Yetmiş dokuz olgu (%50) çoklu ilaç alımı ile başvurdu. Acil servise ortalama başvuru süresi ilaç alımından itibaren 3,9 saat idi. Hiçbir olguda miyokard hasarı açısından belirgin elektrokardiyografik değişiklikler saptanmadı. Ancak, üç hastada QRS mesafesinde hafif genişleme ve QT uzaması tespit edildi. Otuz altı olguda yüksek miyoglobin düzeyi, iki olguda yüksek CK-MB düzeyi bulundu. Artmış yüksek duyarlı troponin I seviyesi, sadece aşırı dozda asetil salisilik asit ve mianserin alan bir vakada saptandı. **Sonuç:** Çocuklarda intihar amaçlı aşırı dozda ilaç alımı ile kardiyak komplikasyonlar ortaya çıkabilir. Bu hayati durumu tespit etmek için yüksek klinik şüphe ile birlikte, elektrokardiyografik değerlendirme ve kardiyak biyobelirteçlerin ölçümü gereklidir.

Anahtar Kelimeler: Kardiyotoksisite; aşırı doz ilaç alımı; çocukluk çağı; intihar

Suicide has increased worldwide in the last half century.[1] Unfortunately, this condition is valid not only in adults but also in pediatric age groups. In some developed countries, suicide is one of the leading causes of death in children and adolescents.[2-4]

Various drugs including antipsychotics, nonsteroidal anti-inflammatory drugs (NSAID), sedative-hypnotic drugs, etc. which are used by parents and other family members are accessible for children. For that reason, one of the most common method in

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suicide attempt among children in Turkey is overdose mono or multi drug intake.[4,5] It is important to know the side effects of drugs on organs/systems and theuraphetic approach to these cases.

Hepatotoxicity or nephrotoxicity following various drug toxications are well studied, however, data regarding cardiotoxicity is limited and reported in adults.[6-8] The possible mechanisms of cardiotoxicity could be described as; direct toxic myocarditis or metabolic changes and/or a part of multi organ system failure due to drug's effect.[7,9,10]

The aim of this study is to evaluate the cardiac enzyme levels during the follow-up period in the hospital as well as to asses demographic, clinical and laboratory patterns of children who had suicidal attempt by drug overdose. The present study should take a worthy particular attention due to being the first study which evaluates cardiotoxicity in suicidal attempt of pediatric age group.

MATERIAL AND METHODS

Over a three years period -between January 2016 and April 2019- patients under the age of 18 with suicidal attempt by taking overdose drug and / or toxic substance who were admitted to the Pediatric Emergency Department of Keçiören Training and Research Hospital were reviewed retrospectively. The children with suicidal attempt but who did not take toxic dose drug and those who are known to have any cardiac disorder previously were excluded from the study. Data were collected from hospital reports at the time of emergency admission and/or during hospitalization.

The variables of the study were demographic features of the patients, medical procedures applied to the patient at first admission in the emergency room, the patient's routine laboratory findings of biochemistry (electrolytes, urea, creatinine, transaminases, bilirubin, albumin, protein), the electrocardiographic (ECG) findings and serum levels of high sensitive troponin I (hsTnI), creatin phosphokinase including myocardial band (CK-MB) and myoblobin.

The data were recorded with the Statistical Package for the Social Sciences program version 21 (SPSS, SPSS Inc, Chicago, IL, USA). The distributions of continuous variables were analyzed with Shapiro Wilk test. The descriptive statistics were defined as mean ± standard deviation for normally distributed data and as median (minimum-maximum) for non-normally distributed data. The difference in the distributions was checked by Chi-square test, $p < 0.05$ was taken as the limit value of significance.

The present study was approved by the scientific committe of Keçiören Training and Research Hospital (date: 04.09.2019-number: 43278876-929) and performed in accordance with the principles of Declaration of Helsinki. Written informed consent was obtained in advance of the study from the parents of the study participants.

RESULTS

A total number of 158 children with suicidal attempt were admitted to pediatric emergency department between the years of 2016 and 2019. The average age was 15.5±1.4 (7-17) years. Of these 158 cases, 82.3% (130) were girls, and the incidence of suicide was found to be significantly higher in girls ($p < 0.001$).

Seventy children attempted suicidal event by taking monodrug overdose while 79 had multidrug and 9 children had taken toxic substances (pesticide, rat poison, alcohol, etc).

Of 79 who took multidrug, 35 reported taking two different types of drugs, 22 reported three, 14 reported four, 3 reported five, 2 reported six and 3 adolescents reported seven types of drugs.

Drugs taken for suicide were grouped according to oral notification or empty medication boxes brought by the patients' relatives are listed in Table 1.

The mean duration of admission to the emergency room was 3.9 hours after drug intake (minimum 10 minutes, maximum 41 hours) and 122 cases (77.2%) were admitted to the emergency department within the first three hours.

A total of 123 cases did not report any symptoms while 13 reported gastrointestinal complaints like nausea, vomiting, dyspepsia. Thirty three cases had neurologic symptoms including lethargy, confusion, vertigo, walking and speech difficulties and one case was unconscious at the time of admission.

TABLE 1: Drug groups reported for suicide attempt.

Drug groups	Number of cases	Ingredients
NSAID	44	Ibuprofen, diclofenac, acetylsalicylic acid, naproxen, etc
Antibiotics, antiprotozoal, antifungal	13	Amoxicillin clavulanic acid, cephalexin, clarithromycin, moxifloxacin, metronidazole, terbinafine, ornidazole, hydroxychloroquine sulfate, etc.
CNS effective drugs, psychiatric drugs	41	Fluoxetine, escitalopram, sertraline, quetiapine,olanzapine, risperidone, valproic acid, pregabalin, carpamazepine, diazepam, methylphenidat, etc.
Muscle relaxants and combinations	15	Phenyramidol hydrochloride, mephenoxalone paracetamol, thiocolchicoside, tizanidine, etc.
Antihistaminic drugs	8	Fexofenadine, rupatadine, cetirizine, levocetirizine, doxylamine
Antihypertensive drugs	7	Zofenopril, perindopril, enalapril, amilodipin, valsartan, etc.
Paracetamol	24	Paracetamol
Antiflu drug combinations	34	Paracetamol + pseudoephedrine + dextromethorphan, ibuprofen + pseudoephedrine, paracetamol +caffeine, etc.
Antidiabetic drugs	3	Metformine
GIS drugs	23	PPI, metpamid, simethicone, hyoscine- N-butylbromide, gaviscon, creon, ursofalk, bismuth, loperamide, etc.
Asthma drugs	5	Salbutamol, terbutaline, theophylline, montelukast
Other drugs	22	Iron preparations, vitamin B, folic acid, oxolamine, erdosteine, benzydamine, oxybutynin hydrochlorid, levothyroxine, colchicine, atorvastatin, enoxaparin, propranolol
Unknown	9	

NSAID: Nonsteroid anti-inflammatory drug, CNS: Central nervous system, PPI: Proton pump inhibitor, GIS: Gastrointestinal system.

Ninety cases underwent gastric lavage, 103 cases were given active charcoal. These patients were treated with intravenous fluid and antiacid therapy during emergency treatment. N-acetyl-cysteine was given to 7 cases with parasetamol overdose. One patient was given diazepam treatment because of atypical seizure and confusion due to serotonin reuptake inhibitor (amitriptyline) overdose (Table 2).

The mean systolic blood pressure was 112 mm Hg and diastolic was 68 mmHg at the time of admission. A total of 11 cases had only systolic hypertension (above than 95% percentile according to age). One case had only diastolic hypertension. Four cases had both systolic and diastolic hypertension.

In terms of renal function tests, only urea values were high in one case and one patient had high urea and creatinine levels. This case was diagnosed as acute renal failure due to high dose of bismuth. Blood, sodium, potassium and calcium levels were normal in all cases. In terms of liver function tests, one patient had elevated aminotransferase elevation, whereas aspartate aminotransferase elevation alone was detected in two cases.

All cases with suicide attempt were evaluated with ECG and no arrhythmia, Q wave, or obvious ST elevation were noted. However, mild QRS widening with 100 msn (upper limit according to age) was present in one patient who took overdose amitriptylin. In addition, QT prolongation was detected in two patients. One of them took overdose olanzapine, the other could not report the exact agent. Sinus tachycardia was detected in 15 patients according to age limits of heart rate.

In terms of cardiac markers, elevated myoglobin level was detected in 36 cases whereas only two cases had elevated CK-MB levels. Despite elevated CK-MB levels, troponin levels were in normal range in these two cases. Only one case who took overdose acetylsalicylic acid and mianserin (a tetracyclic antidepressant agent) had high level of hsTnI. This patient had no ECG changes during admission and ten hours after admission hsTnI level was in normal range. Cardiac marker levels of the participants were demonstrated in Table 3.

A total of 56 cases (35.4%) were treated and completed observation time at pediatric emergency service. Seventy eight cases (49.4%) were hospital-

TABLE 2: Clinical features of study participants.

	Study group (n=158) n (%)
Age (year)	15.5±1.4
Gender (female/male)	130/28 (82.3/17.7)
Number of drugs (mono/multi)	70/79 (44.3/49.6)
Duration of emergency admission (< 3 hours / >3 hours)	122/36 (77.2/22.8)
Symptoms	
Gastrointestinal symptoms	13 (8.2)
Neurologic symptoms	33 (20.8)
Asymptomatic	123 (77.8)
Treatment	
Gastric lavage	90 (56.9)
Active choarcoal	103 (65.1)
N acetyl cysteine	7 (4.4)
Diazepam	1 (0.6)
Results	
Discharged form emergency department	56 (35.4)
Hospitalized	78 (49.4)
Transferred to intensive care unit	23 (14.6)
Discharged with parents' wish	1 (0.6)

TABLE 3: Cardiac biomarker levels at the time of admission.

Parameters	Mean	Minimum	Maximum	Normal range
CK-MB (ng/ml)	1.08	0.2	12	0-5.2
Myoglobin (ng/dl)	45.2	10.3	220	0-43.3
hsTn I(pg/ml)	1.08	0	37.6	0-15.6

CK-MB: Creatin phosphokinase including myocardial band; hsTnI: High sensitive troponin I.

ized at pediatric services after emergency admission. Twenty three cases (14.6%) were transferred other centers due to the need of intensive care unit.

DISCUSSION

Suicide attempt by drug overdose in children and adolescents is a major health problem.[4,11] Although, there is a well-documented increase in suicide attempt among children, knowledge of the effects of these drugs on children's organs/ systems in overdose usage are very limited. Especially, cardiac complications are usually not appreciated by the clinicians in suicidal attempt by drug overdose patients.

It is a well known fact that the heart is physiologically and structurally very sensitive to the adverse effects of drugs. In addition, a large proportion of frequently used drugs have cardiotoxic effects.[12] However, cardiotoxicity due to suicide attempt by drug overdose has been reported in a few previous case reports and these reports included only one specific drug's effect and none of these cases were in pediatric age.[6,8,13] Hypothesized mechanisms for cardiac involvement were; drug's direct toxic effect to myocardium or indirect effect that could be explained by ischemic and metabolic changes due to drug overdose.[6,7] Another rare explanation is that suicide attempt might have important risk factors in development of stress cardiomyopathy named Takatsubo cardiomyopathy.[14] These reports showed evidence of cardiotoxicity by ECG changes and/or elevated cardiac enzymes and/or echocardiography.

In the present study, we evaluated myocardial injury by assessing through ECG and cardiac biochemical markers including hsTnI, myoglobin, CK-MB.

In this study, while there were 36 cases with elevated myoglobin levels and two cases with high CK-MB levels, only one patient had elevated hsTnI level at the time of admission. In fact, this difference in cardiac markers levels was because the sensitivity of markers detecting myocardial damage.

It is well known that myoglobin is a cytoplasmic protein not only in cardiac but also in skeletal muscle and CK-MB may be expressed in up to 20% of total creatin kinase activity in human skeletal muscle. Therefore both of them are not 100% specific for the heart. So that, troponin I is considered as the gold standard for detecting mycardial injury even in pediatric population.[15]

One patient with mildly elevated hsTnI (34 pg/ml-with upper range of 15.6 pg/ml-) level took overdose acetylsalicylic acid and mianserin and had no ECG changes at the time of admission. And ten hours after admission, hsTnI level was in normal range. The apparent myocardial injury as evidenced by the elevation in troponin I without electrocardiographic finding in the present case was of particular interest. This short term injury may have been due to increased cardiovascular workload due to acute stress and sympathetic overactivity rather than the drugs' effect. Because this patient had admitted to the hospital within one hour and treated immediately.

In this study, the mean duration of admission to the emergency room was 3.9 hours after drug intake and 122 cases (77.2%) were admitted to the emergency department within the first three hours. It is known that the most important factor that reduces mortality and morbidity in suicide attempt is early admission to the emergency services and early intervention. In this study, elevated hsTnI except one patient was found because the majority of patients were admitted to the hospital in three hours and also treated in the early period. However, we also detected ECG changes which point out conduction anomaly in three patients. This is also an important finding because especially central nervous system effective drugs lead conduction disturbances which can be resulted in serious cardiac arrhytmias and early detection of them could be lifesaving.[16]

In terms of demographic features of the present study, the incidence of suicide attempt was found to be significantly higher in girls with the incidence of 82.3% (130) and the majority of cases age were in 15-18 age range similarly to previous reports.[3,4,17]

This is because girls have tendency to suffer from major depression more than boys and children younger than 15 years of age less frequently suffer from psychiatric disorders, family conflicts, or romantic disappointment.

Nonsteroid anti-inflammatory drug overdose was the most common cause of suicide attempt in our cases. A similar epidemiological childhood study about suicidal attempt also found NSAI drugs as the most common drug in suicidal attempt by drug overdose.[18] Because these drugs are used by parents and other family members and easy to access. NSAI drugs usually have side effects on gastrointestinal system ,this may be another reason why we could not detect serious cardiotoxicity in our cases.

LIMITATIONS

The limitations of the present study include small sample size, absence of echocardiographic evaluation and follow- up results.

Further prospective studies with large samples including echocardiographic evaluation is necessary to make a certain suggestion. However, this study is important to pull attention to cardiotoxicity in suicide attempt which usually is not appreciated by the clinicians.

CONCLUSION

Suicide attempt by drug overdose is associated with cardiac complications due to heart's well known susceptibility to drug effects with its high energy metabolism. Thus, we believe that along with initial evaluation and treatment, cardiac evaluation with ECG and cardiac biomarkers should be done which may reduce the probable cardiac side effects resulted in serious morbidity or mortality in these cases.

Source of Finance

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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.

Author contributions

***Idea/Concept**: Şeyma Kayalı; **Design:** Şeyma Kayalı; **Control/Supervision:** Şeyma Kayalı; **Data Collection and/or Processing**: Nuran Belder; **Analysis and/ or Interpretation:** Nuran Belder; **Literature Review**: Nuran Belder; **Writing the Article:** Şeyma Kayalı **Critical Review**: Şeyma Kayalı; **References and Fundings:** Nuran Belder; **Materials:** Şeyma Kayalı.*

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