Retrospective Review of Cases of Intoxication in Medical Intensive Care Unit

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ABSTRACT
Objective: Intoxication is a major public health concern worldwide. The aim of our study was to evaluate cases of intoxication in medical intensive care unit (ICU) in terms of demographics characteristics, complications, treatments employed, and mortality.

Methods: This was a retrospective, single-center, observational, descriptive study. The sample included patients over 18 years of age who had been diagnosed with intoxication in the medical ICU between July 1, 2018, and June 30, 2019. Patients’ demographic characteristics, laboratory values, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, poisoning severity scores, Glasgow Coma Scale (GCS) scores, complications developed, and clinical courses were reviewed. The primary outcome was 28-day mortality.

Results: Eighty three patients were enrolled in this study. By sex, 56.6% of the patients were female and 43.4% male. Toxic agent exposure was unintentional in 25.3% of patients but associated with attempted suicide in 74.7%. The causative agents were drugs (72.3%), mushroom (15.7%), methyl alcohol (8.4%), and pesticides (3.6%). Analgesics and anti-inflammatory agents were most common causative agents among intoxication cases. The 28-day mortality was 4.8%. In all non-survivors, cause of death was methyl alcohol intoxication.

Conclusion: Intoxication was most commonly observed in young, married women, most commonly caused by drugs, and most often associated with attempted suicide.

Keywords: Intoxication; Intensive care; Mortality; Poisoning

Introduction
Intoxication is the most important public health problem worldwide and is a major cause of morbidity and mortality, whether intentionally (e.g., attempted suicide) or unintentionally, due to exposure to either legal or illicit substances (1–5). Intoxications account for 0.7–2.4% of emergency department visits (6, 7), and in cases of acute intoxication, 4.1–30.8% of cases are admitted to medical intensive care units (ICU) (8). Toxic substances can be taken via oral, respiratory, cutaneous, parenteral, ocular, and rectal routes (9).

In adults, toxic exposure is caused by analgesics (11.59%), sedative/hypnotic agents (10.14%), antidepressants (6.96%), cardiovascular agents (6.28%), cleaning agents (5.43%), alcohol (4.76%), and pesticides (3.52%) (9).

Intoxication can be asymptomatic; however, it may cause life-threatening symptoms as well. Opiate, cholinergic, sympathomimetic, anti-cholinergic or sedative-hypnotic syndromes may develop based on toxic agent exposed (10). In such cases, rapid, symptomatic treatment can be life-saving. According to 2017 data, our hospital has the highest admission rates in Turkey. Also our hospital is a reference center for intoxications. From the beginning of our study until May 2020, we searched the studies on this subject in PUBMED, TR index, google scholar. In Turkey, many studies have been conducted on intoxication; however, few have examined cases of intoxication treated at ICUs. Thus, the aim of our study was to investigate cases of intoxication admitted to the medical ICU, with particular focus on the patients’ demographic characteristics, seasonal variation, complications, treatments modalities and mortality. It is thought that this study will contribute data on intoxication and in reducing intoxication rate, mortality and morbidity via appropriate measures by raising awareness about intoxication.
Materials and Methods

Study design and setting
This was a retrospective, single-center, observational, descriptive study. Following approval by the local Clinical Research Ethics Committee, the study was conducted in the Medical ICU. The study was performed in accordance with the ethical rules stated in the 1964 Helsinki Declaration, and its subsequent amendments.

Study population and data collection
The patients included to the study were over 18 years of age who had been diagnosed with intoxication in the medical ICU between July 1, 2018, and June 30, 2019. Patients were included in the study only once. We identified the exact poisoning agent(s) from the patient’s history, the drug boxes brought with her/him, according to the pharmacy documentation. The diagnosis was confirmed by measuring the blood paracetamol level of patients with a history of paracetamol intake. Patients with an uncertain history were not included in the study. The following data were retrospectively recorded from the patients’ files, clinical data sheets, and hospital information management system; demographic characteristics, agent of intoxication, mechanism of exposure, arrival time to the hospital, month of presentation, routine laboratory tests performed, comorbid conditions, Acute Physiology and Chronic Health Evaluation (APACHE) II score, poisoning severity score, Glasgow Coma Scale (GCS) score, vital signs at the medical ICU (i.e., body temperature, heart rate, respiration rate, and blood pressure), complications, organ failure (i.e., whether developed or not), hemodialysis indication (i.e., whether present or not), liver transplantation (i.e., whether indicated or not), treatment, need for mechanical ventilation, 28 day-mortality, length of ICU stay, and length of hospital stay.

Statistical analysis
Normal distribution was assessed using visual (i.e., a histogram and odd graphics) and analytic methods (i.e., Kolmogorov–Smirnov test, skewness, kurtosis, and M-to-SD ratio). In this paper, all parameters are presented as mean ± SD, median (25th-75th percentile), or percent, as appropriate. Continuous variables were analyzed using Student’s t test or Mann–Whitney U test, whereas categorical variables were analyzed using chi-square or Fisher’s exact test. Any p value less than .05 was considered to be statistically significant. All calculations were performed in the Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic characteristics of patients and features of agents causing intoxication
During the 12-month study period, 963 patients older than 18 years of age admitted to the medical ICU, 83 were diagnosed with intoxication (8.6%). Table 1 summarizes the patients’ demographic characteristics and features of the responsible intoxication agents. Two patients were pregnant, and 17 patients (81%) with psychiatric disorders was included with attempted suicide. The 28-day mortality was 4.8%. According to poisoning severity score, 51.8% of patients had no symptoms, 26.5% had minor symptoms, 12.0% had moderate symptoms, and 4.8% had severe symptoms.

| Table 1. Demographic characteristics of patients and features of agents causing intoxication |
|-----------------------------------------------|
| Variable                                      | n = 83 |
| Sex                                           |       |
| Female                                        | 47 (56.6) |
| Male                                          | 36 (43.3) |
| Ages (years)                                  | 32 (23-40) |
| Time to presentation (min)                    | 180 (90-420) |
| Type of intoxication                          |       |
| Suicide                                       | 62 (74.7) |
| Unintentional                                  | 21 (25.3) |
| Type of exposure                              |       |
| Oral                                          | 81 (97.6) |
| Subcutaneous                                   | 2 (2.4) |
| History of previous intoxication              |       |
| Number of previous intoxication               |       |
| 0                                             | 77 (92.8) |
| 2                                             | 3 (3.6) |
| 3                                             | 2 (2.4) |
| 4                                             | 1 (1.2) |
| Smoking                                       |       |
| Yes                                           | 36 (43.4) |
| No                                            | 15 (18.1) |
| Alcohol consumption                           |       |
| Yes                                           | 33 (39.8) |
| No                                            | 9 (10.8) |
| Marital status                                |       |
| Married                                       | 48 (57.8) |
| Single                                        | 25 (30.1) |
| Widowed                                       | 10 (12) |
| Education                                     |       |
| Primary school                                | 33 (39.8) |
| Secondary school                              | 9 (10.8) |
| High school                                   | 12 (14.3) |
| University                                    | 5 (6) |
| Unknown                                       | 20 (24.1) |
| History of psychiatric disease                |       |
| Yes                                           | 21 (25.3) |
| No                                            | 36 (43.4) |
| Charlson comorbidity index                     |       |
| 0                                             | 72 (86.7) |
| 1                                             | 4 (4.8) |
| 2                                             | 4 (4.8) |
| 3                                             | 2 (2.4) |
| 6                                             | 1 (1.2) |
| APACHE II score                               | 6 (1-36) |
| Poisoning severity score                      |       |
| 0                                             | 43 (51.8) |
| 1                                             | 22 (26.5) |
| 2                                             | 10 (12) |
| 3                                             | 4 (4.8) |
| 4                                             | 4 (4.8) |
| Intoxication etiology                         |       |
| Drugs                                         | 60 (72.3) |
| Mushroom                                      | 13 (15.7) |
| Pesticides                                    | 7 (8.4) |
| Alcohol                                       | 3 (3.6) |
| Drug intoxications                            |       |
| Single agent                                   | 22 (36.7) |
| Multiple agents                                | 28 (43.6) |
| Drug groups                                   |       |
| Analgesic and anti-inflammatory agents         | 27 (32.1) |
| Antimicrobial agents                           | 11 (10.7) |
| Antidepressant and antipsychotic agents        | 10 (9.7) |
| Cardiovascular agents                         | 14 (16.3) |
| Oral anti-diabetics and insulin                | 6 (5.8) |
| Other agents                                   | 35 (42.2) |

Values are presented as number (%) of patients or median (25th-75th percentile). APACHE II score: Acute Physiology and Chronic Health Evaluation II Score.
In four groups of patients stratified by age, intoxication was most common among 18–24 year olds (Figure 1).

In the cases of intoxication associated with attempted suicide, 32 patients (51.6%) were married, 21 (33.9%) were single, and nine (14.5%) were widowed. Of the same cases, blood group was “0” in 33.8%, “A” in 25.8%, “B” in 8.1% and “AB” in 14.5%, whereas the blood group of 17.7% was unknown.

By sex, female patients in this study were significantly younger than males (p < .05), and their intoxication was more commonly associated with attempted suicide (Table 2).

Table 2. Characteristics of patients by sex

| Variable                  | Female (n=47) | Male (n=36) | P-value |
|---------------------------|---------------|-------------|---------|
| Age                       | 28 (21-37)    | 36 (23.25-47.75) | 0.025   |
| Intoxication due to suicide| 40 (85.1)     | 22 (61.1)   | 0.022   |
| Unintentional intoxication | 7 (14.9)      | 14 (38.9)   | 0.127   |

Values are presented as (25th-75th percentile) or number (%) of patients.

Seasonal distribution of intoxication

By seasonal distribution, intoxication had occurred in the sample most commonly in the summer (n = 29, 34.9%), followed by the spring (n = 22, 26.5%), winter (n = 18, 21.7%), and autumn (n = 14, 16.9%). Of the patients with mushroom intoxication, 7 (53.8%) were admitted in the summer, three (23.1%) in the spring, and the other three (23.1%) in the autumn.

Clinical courses and treatments

Potential complications in the patients were assessed according to toxic agent. The complications developed were hypotension, bradycardia, tachycardia, shock, hypoglycemia, altered mental status, lactic acidosis, renal failure, hepatic failure, loss of vision, and drug allergy. Meanwhile, organ failures developed were renal, hepatic, and respiratory failure. Patients who experienced hepatic failure did not require liver transplantation. Table 3 summarizes the patient’s clinical courses and treatments.

Organ failure, complications and need for hemodialysis, invasive mechanical ventilation and vasopressor were observed in all non-survivors. Methyl alcohol was the causative agent in non-survivors.

Table 3. Clinical course and treatments

| Variable                          | n=83   |
|-----------------------------------|--------|
| Complication development          | 21 (25.3) |
| Hemodialysis need                 | 9 (10.8)  |
| Invasive mechanical ventilation   | 5 (6)    |
| need                              |         |
| Vasopressor need                  | 10 (12)  |
| Treatments                        |         |
| Active charcoal                   | 11 (13.3) |
| N-acetyl cysteine                 | 26 (31)   |
| Silymarin                         | 12 (14)   |
| Ethyl alcohol                     | 7 (8)     |
| Fomepizole                        | 1 (1.2)   |
| Glucagon                          | 2 (2.4)   |
| Length of ICU stay (days)         | 3 (2-4)   |
| Mode of discharge from ICU        |         |
| Transfer to psychiatric clinic     | 12 (14.5) |
| Transfer to internal medicine clinic| 13 (15.7) |
| Discharge from hospital           | 54 (65.1) |
| Death                             | 4 (4.8)   |
| Length of hospital stay (days)    | 3 (2-4)   |
| Mode of discharge from hospital   |         |
| By request of patient/relatives   | 25 (30.1) |
| By recovery                       | 51 (61.4) |
| Referral                          | 3 (3.6)   |
| Death                             | 4 (4.8)   |

Values are presented as number (%) of patients or (25th-75th percentile). ICU: Intensive Care Unit.

Patients’ characteristics and laboratory findings according to survival

Table 4 summarizes the patients’ characteristics and laboratory findings according to whether they survived intoxication. However, we did not make statistical comparisons between the two groups because the characteristics of the two groups, the time of admission, the causative agents and the amount of toxic exposure were different. All non-survivors were male, and in all non-survivors, cause of death was methyl alcohol intoxication.

Discussion

An important cause of morbidity and mortality worldwide, intoxication is responsible for a significant portion of patient admissions at emergency departments. The type and amount of toxic substance, along with time of ingestion and exposure, are critical pieces of information for managing patients with intoxication. However, anamnesis may not always be accurate, and in some cases, the toxic effects of substances cannot be predicted. Clinicians refer patients with intoxication to ICUs based on their experience, findings in available literature, the patient’s specific clinical presentation, and the recommendations of the National Poison Information Center in Turkey. In past studies, intoxication has been found to account for 1.8–13.8% of admissions to ICUs from emergency departments (8, 11–15). In our study, the intoxication rate was similar with the literature.

In Yaylaci et al.’s study, the mean age of patients with intoxication was 29.4 ± 11.0 years, and 68% were female (8). By contrast, in Liisanantti et al.’s study, mean age was 39.7 years, and 53% of patients were female (16). In our study, most of the patients were young and female.
cases of intoxication are most commonly reported following oral exposure (5, 9). In our study, the oral route was also the most common route of exposure.

The literature additionally shows that intoxication is more common among married individuals. In Mete et al.’s study, 64.9% of patients with intoxication were married, while 59.2% were married in Avsarogullari et al.’s study (15, 22). By contrast, Ozkose et al. reported that 36.4% of patients were married, whereas 61.8% were single (6). Similar to these studies, the majority of our patients were married (15, 22). We think that the reasons why intoxications are more common in young, married women are related to family or social pressure, socioeconomic conditions.

The rate of intoxication was highest among primary-school graduates in our study, which suggests that the rate of intoxication increases as the level of education decreases. However, because level of education could not be retrospectively determined in 25.3% of patients in our study, drawing any definitive conclusion is impossible.

A history of psychiatric disorder was found in 9.2% of patients with intoxication in Yaylaci et al.’s study and 35.3% in Kose et al.’s study (8, 23). In those studies, most cases of intoxication were associated with attempted suicide specifically among patients with a history of psychiatric disease. In our study, 25.3% of patients had a history of psychiatric disease, and in the vast majority of them, intoxication was also associated with attempted suicide. This may be due to treatment-resistant depressive disorders.

Lester’s (1987) findings suggest that suicide may be less common in populations with a higher prevalence of individuals with O blood group and more common in populations with a higher prevalence of individuals with AB blood group (24). In our study, patients with intoxication associated with attempted suicide most commonly displayed O blood group. The difference may be due to the limited number of cases, racial variation, regional variation, and blood polymorphism more than the prevalence of ABO blood group.

Yaylaci et al. in their study assessing cases of intoxication treated in ICU found that the cause of intoxication was drugs in 88.2% of cases, rat poison and pesticides in 8.5%, food and mushroom in 1.3%, alcohol in 1.3%, and toxic gas in 0.6% (8). In cases attributed to drugs, 34.8% involved more than one agent, 34.0% involved antidepressant-antipsychotic agents, and 14.8% involved analgesics.

Akbaba et al. found that the most common cause of intoxication in their study was drugs (71.1%), followed by pesticides (18.9%), foods (3.7%), caustic agents (3.1%), carbon monoxide (1.8%), and alcohol (1.4%) (7). Among drugs assessed, the most common agents were psychoactive substances (51.6%) and analgesics (22.1%).

In a study conducted at Ankara province, Ozkose et al. found that cause of intoxication was drugs in 75.8%, carbon monoxide in 17.6%, foods in 2.6%, corrosive agents in 2.2%, pesticides in 0.9% and alcohol in 0.9% of patients (6). When drug groups were assessed, it was seen that intoxication occurred with single agent in 74% and multiple agents in 26% of patients. While drugs included analgesics in 30.1%, psychoactive agents in 20.8%, antibiotics in 6.4%, other drugs in 5.8%, cardiovascular agents in 4.1% and antihistamines in 3.4% of patients.

| Variable                       | Survivor (n=79) | Non-survivor (n=4) |
|--------------------------------|----------------|-------------------|
| **Sex**                        |                |                   |
| Female                         | 47 (59.5)      | 4 (100)           |
| Male                           | 32 (40.5)      |                   |
| **Cause of intoxication**      |                |                   |
| Drug                           | 60 (75.9)      |                   |
| Fungal                         | 13 (16.5)      | 1 (25)            |
| Pesticide                      | 3 (3.8)        |                   |
| Alcohol                        | 3 (3.8)        | 1 (25)            |
| **Vital signs**                |                |                   |
| Body temperature (°C)          | 36.6±0.38      | 36.6±0.93         |
| Heart rate (beat/min)         | 87.4±15.2      | 104.5±23.6        |
| Mean arterial pressure (mmHg) | 89.1±16.4      | 88.3±6.7          |
| Respiration rate (respiration/min) | 20.5±3.5        | 23.8±11.1         |
| **APACHE II score**           | 14 (4-14)      | 3 (3-3)           |
| **WBC (10³/µL)**              | 265.6±75.2     | 263.2±202.2       |
| **Hb (g/dL)**                  | 103 (33-11)    | 198.4±3.45        |
| **Glucose (mg/dL)**           | 104 (91-121)   | 169 (91-288)      |
| Serum creatinine (mg/dL)       | 0.7 (0.6-0.89) | 1.73 (1.24-2.37)  |
| Serum sodium (mmol/L)         | 130 (137-140)  | 136.5 (131-139)   |
| Serum potassium (mmol/L)       | 4.1 (3.8-4.5)  | 5.7 (3.9-6.9)     |
| Serum chloride (mmol/L)        | 103 (102-106)  | 97.5 (90.3-101)   |
| Creatinine kinase (U/L)       | 99 (81-137)    | 77 (73-)          |
| Lactate dehydrogenase (U/L)   | 272 (197-300)  | 317.5 (246-445)   |
| AST (U/L)                      | 19 (16-26)     | 35.5 (17-69)      |
| ALT (U/L)                      | 15 (12-24)     | 16 (11-23)        |
| **INR**                        | 1.2±0.14       | 1.4±0.21          |
| **Platelet (10³/µL)**          | 104 (91-121)   | 169 (91-288)      |
| **APTT (secnd)**               | 7.4 (7.36-7.42)| 6.91 (6.7-7.2)   |
| **pH**                         | 4.02 (35.46-44)| 53 (24-78)        |
| **HCO₃ (mmol/L)**              | 23.7 (22.1-25.3)| 11.7 (5.5-17.8) |
| **Lactate (mmol/L)**           | 1.2 (0.8-18)   | 9.35 (2.6-13.8)  |

|     | Survivor (n=79) | Non-survivor (n=4) |
|-----|----------------|-------------------|
| **Numbers are presented as number (%) of patients, mean ± standard deviation or (25%-75th percentile).** | | |
| **GCS**: Glasgow coma scale. **APACHE II score**: Acute Physiology and Chronic Health Evaluation II Score. **WBC**: White Blood Cell. **Hb**: Hemoglobin. **AST**: Aspartate aminotransferase. **ALT**: Alanine aminotransferase. **INR**: International Normalization Ratio. **aPTT**: Activated partial thromboplastin time. **PCO₂**: Partial carbon dioxide pressure. **HCO₃**: Bicarbonate | | |
| **Time from exposure to admission to the hospital, 74.7% of patients in Canakci et al.’s study presented within 6 hour (hr), whereas 63.2% presented within 5 hr in Kekce et al.’s study and 50.8% in 2 hr in Aydin et al.’s study (14, 17, 18). Yesil et al. found that mean time to hospital admission was 7.61 hr, whereas Ozyar et al. reported a mean of 4.4 hr (19, 20). In our study, median time to hospital admission after toxic agent exposure was 3 hr.** | | |
| **In our study’s sample, intoxication was most commonly associated with attempted suicide, which has been the case in other studies conducted in Turkey and around the world (6, 8, 9, 21). Also in our study, intoxication associated with attempted suicide was more common among females than males.** | | |
| **Toxic agents can be taken via oral, respiratory, cutaneous, parenteral, ocular, and rectal routes. In the literature, cases of intoxication are most commonly reported following oral exposure (5, 9). In our study, the oral route was also the most common route of exposure.** | | |
In our study, it was seen that drugs were most common cause of intoxication as multiple drug ingestion being most common. According to drug group, analgesics and anti-inflammatory agents were most common agents, followed by cardiovascular agents, perhaps because analgesics are over-the-counter drugs, as well as prescribed for many conditions, which makes them readily available. In our study, all patients with intoxication with alcohol were male. Another study conducted in 2018 found the similar results (21). The reason for this situation; it may be due to the fact that men consume more alcohol than women, and men have easier access to alcohol.

Destegul et al. observed that, by time of year, intoxications occurred most commonly in April (27.5%) and May (11.0%) (21). Yaylaci et al., by contrast, found that intoxications were most common in the winter (33.3%), followed by spring (25.5%), summer (21.6%), and autumn (19.6%) (8). In a study by Aydin et al., it was found that intoxication cases most commonly occurred in May (15.5%) while least commonly in December (3.2%) (18). In our study, cases of intoxication due to food occurred only in May and June.

In an extension of those findings, Deisenheimer et al. investigated the relationship between suicide and time of year. Among their results, suicides occurred more often during the spring and summer (25), which they suggested may be due to biological factors, especially serotonergic alterations, and the experiences of depressive patients. In our sample, suicides occurred most commonly during the summer. In the light of this information; there may be a relationship between seasons and suicide attempt.

In Destegul et al.’s study, 9.1% of patients required invasive mechanical ventilation (21); that rate was 11% in Christ et al.’s study and 15.3% in Mete et al.’s (13, 15). In our study, the rate of need for mechanical ventilation was lower, for a difference possibly due to variations in the type, amount, and mechanisms of toxic agents.

In the literature, length of ICU stay was reported as 2.4 ± 1.6 days by Yaylaci et al., 3.1 ± 2.4 days by Mete et al., and 32.1 hr by Liisanantti et al. (8, 15, 16). In our study, length of ICU stay was similar with literature.

In Yaylaci et al.’s study, most patients (96.7%) were discharged after recovery, whereas 3.3% were discharged at their request (8). In Destegul et al.’s study, 98.16% of patients were discharged after recovery, 0.91% were transferred to another ICU, and 0.91% died (21). In Mete et al.’s study, 81.6% were discharged, 8.8% were transferred to a psychiatric clinic, and 9.6% died (15). These rates are different in our study; they may be due to differences in the type of toxic agents, the amount of toxic agents, and the hospital admission time.

In all non-survivors in our study, the causative agent of intoxication was methyl alcohol. For all such patients, it was seen hemodialysis was needed due to severe metabolic acidosis and invasive mechanical ventilation was required due to respiratory failure. It was observed that GCS score was lower while APACHE II score was higher in non-survivor group. This finding was similar with literature (14, 16). The APACHE II score represents predicted mortality within first 24 hours after admission to ICU. It is expected to be higher in non-survivors. In patients with methyl alcohol intoxication, metabolic acidosis with elevated anion gap, renal failure and central nervous system findings can be observed. In our study, low GCS score, low bicarbonate level, low serum chloride, and increased serum creatinine is the anticipated presentation in non-survivor group.

**Conclusion**

Intoxication was mostly observed in young, married women and more common among individuals with a lower level of education. Analgesics and anti-inflammatory agents were the most common agents of intoxication, although death occurred only due to complications following methyl alcohol intoxication. Preventing easy access to analgesic and anti-inflammatory agents, improving socioeconomic conditions, providing positive support for psychological needs, and limiting access to methyl alcohol may curb rates of intoxication. Cases of intoxication seem less likely in individuals from well-educated communities with good psychological well-being.
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