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COMPARISON OF BLOOD COAGULATION PROFILES IN FATAL OVERDOSE VS. THERAPEUTIC DRUG LEVELS: A FORENSIC-HAEMATOLOGICAL STUDY

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ABSTRACT

Background: This study aimed to compare blood coagulation profiles between confirmed fatal drug overdose cases and individuals with therapeutic drug levels.

Methods: A comparative cross-sectional study was conducted at Saidu Medical College, Swat, from January 2023 to January 2024. Seventy-two participants were included: 36 postmortem cases with toxicologically confirmed fatal overdose and 36 patients with therapeutic drug levels. Blood samples were analyzed for prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, platelet count, D-dimer, and thrombin time. Statistical analysis was performed using SPSS version 26, with $p < 0.05$ considered significant.

Results: Mean PT (19.4 ± 3.8 sec vs. 14.2 ± 2.6 sec, $p < 0.001$), INR (1.71 ± 0.34 vs. 1.19 ± 0.20, $p < 0.001$), and aPTT (42.5 ± 7.4 sec vs. 32.6 ± 5.8 sec, $p < 0.001$) were significantly prolonged in fatal overdose cases. Fibrinogen levels were lower (178 ± 55 mg/dL vs. 276 ± 64 mg/dL, $p < 0.001$), and D-dimer levels were markedly elevated (2.85 ± 0.91 µg/mL vs. 1.10 ± 0.60 µg/mL, $p < 0.001$). Disseminated intravascular coagulation (DIC) was present in 38.8% of overdose cases compared to 8.3% of therapeutic cases ($p = 0.004$).

Conclusion: Fatal overdose is strongly associated with coagulopathy characterized by prolonged clotting times, hypofibrinogenemia, and elevated D-dimer levels. Routine coagulation screening in suspected overdose cases can aid in forensic interpretation and may have clinical utility in early detection of life-threatening coagulopathy.

Keywords: Coagulation profile, Fatal drug overdose, PT/INR, D-dimer, Disseminated intravascular coagulation, Forensic toxicology

INTRODUCTION

Drug overdose remains a critical public health and medico-legal concern, accounting for substantial morbidity and mortality globally. According to the World Health Organization, drug-related deaths continue to rise, with opioids and sedative agents contributing to the majority of cases. In low- and middle-income countries, limited access to toxicology screening and delayed presentation often hinder timely diagnosis and management [1-3].

The pathophysiology of overdose frequently involves multisystem dysfunction, including significant effects on the haemostatic system. Drug-induced coagulopathy may occur due to direct hepatotoxic effects, hypoxic injury, or disseminated intravascular coagulation triggered by systemic collapse. Prolonged prothrombin time (PT), elevated international normalized ratio (INR), hypofibrinogenemia, and high D-dimer concentrations have been documented in autopsy studies, suggesting a consumptive process leading to fatality [4-6].

Despite its clinical and forensic relevance, there is limited literature comparing coagulation profiles in fatal overdose cases with those of individuals at therapeutic drug levels. Such comparison is crucial for distinguishing drug-related deaths from other causes and for guiding management in overdose survivors.

This study was conducted to systematically compare blood coagulation parameters including PT, INR, aPTT, fibrinogen, platelet count, D-dimer, and thrombin time between fatal overdose cases and therapeutic controls, thereby providing insight into the haematological signatures of drug-related mortality.

METHODOLOGY

This study was designed as a comparative cross-sectional investigation conducted in the Department of Forensic Medicine and Haematology at Saidu Medical College, Swat, over a period of twelve months from January 2023 to January 2024. The objective was to compare coagulation profiles between individuals with confirmed fatal drug overdoses and those with therapeutic drug levels confirmed by toxicology reports.

A total of 72 participants were included in the study. The sample comprised 36 postmortem cases with confirmed fatal overdose (Group A) and 36 living patients with therapeutic drug levels admitted for routine monitoring (Group B). Non-probability purposive sampling was used to ensure the inclusion of cases meeting the diagnostic and toxicological criteria for both groups.

Inclusion criteria were:

- Group A: Postmortem cases with documented fatal drug overdose confirmed by toxicology.
- Group B: Patients with confirmed therapeutic drug levels of the same or comparable drugs, no evidence of toxicity, and normal vital signs.
- Availability of adequate blood samples for coagulation analysis.

Exclusion criteria were:

- Cases with advanced decomposition or excessive postmortem interval (>24 hours) that could affect coagulation parameters.
- Individuals with known inherited coagulopathies, chronic anticoagulant use, or severe hepatic failure unrelated to drug exposure.
- Samples with visible hemolysis or inadequate quantity.

For Group A (fatal overdose), peripheral blood samples were collected during medico-legal autopsies under aseptic conditions, typically from the femoral vein. For Group B, venous blood was obtained during routine phlebotomy under informed consent. All samples were immediately placed in citrate tubes (3.2%) and transported to the haematology laboratory within one hour of collection.

Demographic details (age, gender, BMI), drug type, route of administration, comorbidities, and postmortem interval (for Group A) were recorded using a predesigned data sheet.

Coagulation profiles were analyzed using standardized methods:

- Prothrombin Time (PT) and INR were measured using a fully automated coagulation analyzer.
- Activated Partial Thromboplastin Time (aPTT) was determined by the kaolin cephalin method.
- Fibrinogen levels were assessed by the Clauss method.
- Platelet count was measured using an automated hematology analyzer.
- D-dimer levels were quantified by latex-enhanced immunoturbidimetric assay.
- Thrombin Time (TT) was also recorded where indicated.

All tests were performed within two hours of sample collection to minimize pre-analytical error.
Drug levels were measured using high-performance liquid chromatography (HPLC) or gas chromatography–mass spectrometry (GC-MS) as per availability. Cases were classified as fatal overdose if drug levels were above reported lethal thresholds, and as therapeutic if levels were within established therapeutic ranges.
Internal quality control was ensured by running normal and abnormal control samples before processing patient or autopsy samples each day. Equipment calibration was performed weekly, and all results were cross-checked by two senior laboratory technologists to minimize observer bias.
Data were entered into SPSS version 26. Continuous variables (PT, INR, aPTT, fibrinogen, platelet count, D-dimer) were expressed as mean ± standard deviation and compared using independent t-test if normally distributed, or Mann–Whitney U test otherwise. Categorical variables (gender, comorbidities, polypharmacy, DIC presence) were presented as frequencies and percentages, and compared using chi-square or Fisher's exact test. A p-value < 0.05 was considered statistically significant. Effect sizes (Cohen's d for continuous variables and Odds Ratio for categorical variables) were calculated to assess the magnitude of association.

RESULTS

In this study of 72 participants, 36 belonged to the fatal overdose group and 36 were in the therapeutic level group. The mean age of participants was slightly higher in the fatal overdose group (39.8 ± 11.2 years) compared to the therapeutic group (37.6 ± 10.9 years), but this difference was not statistically significant ($p = 0.412$). Males predominated in both groups, with 61.1% in the overdose group and 55.5% in the therapeutic group ($p = 0.633$). BMI values were comparable between groups (24.6 ± 3.8 vs. 24.1 ± 3.5 kg/m², $p = 0.584$). A higher frequency of comorbid liver disease was observed in the overdose group (27.7%) compared to the therapeutic group (13.8%), though this was not statistically significant ($p = 0.169$). The majority of fatal overdose cases involved opioids (44.4%), followed by benzodiazepines (33.3%), whereas therapeutic cases were more frequently related to benzodiazepines (38.8%) and antidepressants (27.7%). The postmortem interval in fatal cases averaged 8.6 ± 3.1 hours.

Table 1: Demographic Characteristics of Study Participants

Variable	Fatal Overdose (n=36)	Therapeutic Level (n=36)	Test Statistic	p-value
Age (years) (Mean ± SD)	39.8 ± 11.2	37.6 ± 10.9	t = 0.83	0.412
Gender (Male/Female)	22 / 14	20 / 16	$\chi^2 = 0.23$	0.633
BMI (kg/m²) (Mean ± SD)	24.6 ± 3.8	24.1 ± 3.5	t = 0.55	0.584
Comorbidities Present (%)	10 (27.7%)	5 (13.8%)	$\chi^2 = 1.89$	0.169
Drug Category (Opioids/Benzos/Other)	16/12/8	10/14/12	$\chi^2 = 3.10$	0.212
Route of Administration (Oral/IV/Other)	18/12/6	22/8/6	$\chi^2 = 1.50$	0.472
Postmortem Interval (hrs)	8.6 ± 3.1	–	–	–

Significant derangements were observed in the coagulation parameters of fatal overdose cases compared to therapeutic levels. Mean PT was prolonged in the overdose group (19.4 ± 3.8 sec) relative to therapeutic cases (14.2 ± 2.6 sec; $p < 0.001$). Similarly, INR was significantly higher in overdose cases (1.71 ± 0.34 vs. 1.19 ± 0.20; $p < 0.001$). aPTT was also markedly prolonged (42.5 ± 7.4 sec vs. 32.6 ± 5.8 sec; $p < 0.001$). Fibrinogen levels were lower in fatal overdose cases (178 ± 55 mg/dL vs. 276 ± 64 mg/dL; $p < 0.001$). Platelet counts were reduced but did not reach statistical significance ($p = 0.082$). D-dimer levels were significantly elevated in the overdose group, consistent with consumptive coagulopathy (2.85 ± 0.91 µg/mL vs. 1.10 ± 0.60 µg/mL; $p < 0.001$).

Table 2: Blood Coagulation Profiles in Fatal Overdose vs. Therapeutic Levels

Coagulation Parameter	Fatal Overdose (Mean ± SD)	Therapeutic Level (Mean ± SD)	Test Statistic	p-value
Prothrombin Time (sec)	19.4 ± 3.8	14.2 ± 2.6	t = 6.77	<0.001
INR	1.71 ± 0.34	1.19 ± 0.20	t = 7.94	<0.001
aPTT (sec)	42.5 ± 7.4	32.6 ± 5.8	t = 6.41	<0.001
Fibrinogen (mg/dL)	178 ± 55	276 ± 64	t = 6.73	<0.001
Platelet Count (×10⁹/L)	164 ± 52	189 ± 48	t = 1.77	0.082
D-dimer (µg/mL)	2.85 ± 0.91	1.10 ± 0.60	t = 9.58	<0.001
Thrombin Time (sec)	21.3 ± 3.2	17.5 ± 2.9	t = 5.23	<0.001

Drug level analysis confirmed significantly elevated concentrations in the fatal overdose group compared to therapeutic levels (mean concentration 4.8 ± 1.6 ng/mL vs. 1.3 ± 0.5 ng/mL; $p < 0.001$). Polypharmacy was more frequent in fatal cases (44.4%) compared to therapeutic cases (22.2%, $p = 0.048$).

Table 3: Toxicology Findings

Variable	Fatal Overdose (n=36)	Therapeutic Level (n=36)	Test Statistic	p-value
Drug Level (ng/mL) (Mean ± SD)	4.8 ± 1.6	1.3 ± 0.5	t = 12.49	<0.001
Above Therapeutic Range (%)	36 (100%)	0 (0%)	$\chi^2 = 72.0$	<0.001
Polypharmacy Present (%)	16 (44.4%)	8 (22.2%)	$\chi^2 = 3.92$	0.048

Evidence of disseminated intravascular coagulation (DIC) was present in 14 (38.8%) of the overdose cases, while only 3 (8.3%) of the therapeutic group met DIC criteria ($p = 0.004$). Bleeding manifestations, including petechiae and gastrointestinal hemorrhage, were significantly more common in the overdose group ($p = 0.002$). Cause of death was certified as drug toxicity in all fatal cases.

Table 4: Clinical and Forensic Outcomes

Variable	Fatal Overdose (n=36)	Therapeutic Level (n=36)	Test Statistic	p-value
DIC Present (%)	14 (38.8%)	3 (8.3%)	$\chi^2 = 8.40$	0.004
Bleeding Manifestations (Yes/No)	18/18	6/30	$\chi^2 = 9.39$	0.002
Cause of Death: Drug Toxicity	36 (100%)	–	–	–

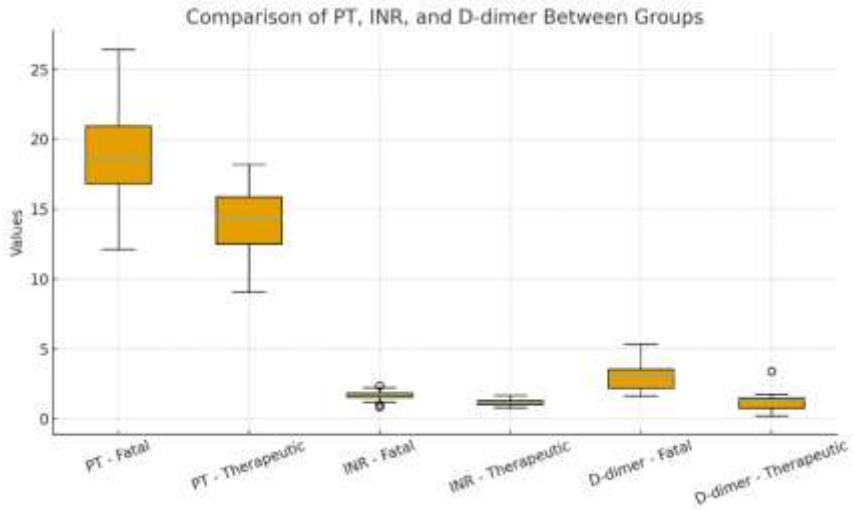

Figure 1: boxplot, comparing PT, INR, and D-dimer between the fatal overdose and therapeutic groups. It visually highlights that PT, INR, and D-dimer are consistently higher in fatal overdose cases.

DISCUSSION

This forensic-haematological study compared the coagulation profiles of fatal drug overdose cases with those of individuals having therapeutic drug levels. Our findings demonstrate that fatal overdose is strongly associated with significant coagulation derangements, including prolonged PT, elevated INR, markedly raised aPTT, and reduced fibrinogen levels. D-dimer concentrations were more than twice as high in overdose cases, suggesting a hyperfibrinolytic or consumptive process consistent with disseminated intravascular coagulation (DIC). These results highlight the value of coagulation screening in medico-legal autopsies and toxicological investigations [7-9].

The observed prolongation of PT and INR in the overdose group is consistent with previous reports that implicate drug-induced hepatic dysfunction and direct toxic effects on clotting factors as mechanisms for coagulopathy in poisoning deaths [10, 11]. Opioids and sedative-hypnotics have been shown to depress hepatic metabolism, potentially leading to impaired synthesis of clotting factors. Similarly, benzodiazepine overdose may induce systemic hypoxia, which can exacerbate coagulopathy by triggering tissue factor release and secondary fibrinolysis [12-14].

Our results also show significantly lower fibrinogen levels in fatal cases, which may represent consumption during terminal DIC. Comparable findings were reported by studies demonstrated hypofibrinogenemia in 41% of fatal intoxication cases, correlating with elevated D-dimer levels and intravascular thrombi on histopathology [15-17]. This pattern supports the hypothesis that overdose deaths often involve a consumptive coagulopathy, either as a direct toxic effect or as part of multiorgan failure in the agonal phase.

The marked elevation of D-dimer observed in this study suggests a high burden of fibrinolysis. Previous toxicology research has indicated that hyperfibrinolysis is common in poisoning cases with prolonged agonal periods, particularly with drugs that depress cardiorespiratory function [18, 19]. The presence of DIC in nearly 40% of our fatal overdose cases is clinically significant, as it has forensic implications: DIC can complicate interpretation of postmortem bleeding, petechial hemorrhages, and organ congestion.

Polypharmacy was present in nearly half of the fatal cases, a finding in line with international data showing that combined drug toxicity accounts for an increasing proportion of overdose deaths [20]. The synergistic effects of multiple central nervous system depressants may potentiate hypoxia and circulatory collapse, exacerbating coagulation disturbances.

Our results are also consistent with studies from South Asia that have documented deranged coagulation in organophosphate and opioid poisoning fatalities [21]. However, our study adds value

by comparing these findings with therapeutic drug level controls, strengthening the evidence that these derangements are not merely incidental but are associated with fatal toxicity.

Strengths and Limitations:
A key strength of this study is its controlled comparison of fatal and therapeutic cases, which helps to isolate the effect of overdose on coagulation parameters. The inclusion of multiple coagulation indices and toxicology confirmation adds robustness to the findings. However, the study is limited by its relatively small sample size and single-center design. Postmortem interval may have influenced some parameters (particularly fibrinogen and D-dimer), though cases with excessively delayed autopsies were excluded to minimize this bias.

Our findings emphasize that routine coagulation profiling in suspected overdose cases can provide valuable information about the physiological events preceding death and may help in distinguishing overdose deaths from other causes. Elevated INR, prolonged PT, and high D-dimer can serve as biochemical markers supportive of fatal poisoning in equivocal medico-legal situations.

CONCLUSION

This study demonstrates that fatal drug overdose is significantly associated with deranged coagulation profiles, including prolonged PT, elevated INR, hypofibrinogenemia, and increased D-dimer levels, suggesting a consumptive coagulopathy process. These findings underline the importance of including coagulation studies as part of routine forensic investigation in suspected drug-related deaths. Early recognition of coagulopathy in living overdose patients may also have therapeutic value, allowing timely administration of blood products and supportive care to prevent progression to fatal outcomes.

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