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Amphetamine-related mortality; a study of postmortem toxicological, pathological, and clinical findings from 2012 to 2022 in Isfahan, Iran

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Abstract

Introduction: Amphetamines represent a widely abused class of drugs globally, with instances of fatalities resulting from inadvertent consumption. Notably, in the year 2008 in Iran, amphetamine emerged as the predominant substance subjected to abuse. Amphetamine induces a spectrum of physiological and psychoactive effects, including heightened arousal, euphoria, diminished fatigue, accelerated heart rate, positive mood, pupil dilation, elevated blood pressure, increased body temperature, behavioral disinhibition, reduced appetite, and heightened alertness. The autopsy and pathological findings associated with fatalities resulting from amphetamine intoxication have garnered limited scrutiny. This study endeavors to characterize and compare the autopsy and pathological findings in amphetamine intoxicated deceased.

Objectives: This study aims to investigate and compare the autopsy and pathological findings in cases of amphetamine-related fatalities. It seeks to provide insights into the toxicological, clinical, and pathological profiles of these cases in Isfahan, Iran, over a decade (2012–2022), contributing to a better understanding of the impacts of amphetamine intoxication.

Materials and Methods: We systematically identified all instances of amphetamine-related fatalities in Isfahan spanning the period from 2012 to 2022, utilizing data derived from the Noor and Ali Asghar Hospital Electronic Medical Report. Comprehensive information pertaining to demographic characteristics, clinical symptoms, autopsy, and pathology was meticulously documented in a checklist for each patient and subjected to thorough analysis.

Results: Between 2012 and 2022, a total of 42 fatalities attributable to amphetamine were identified, encompassing 32 males (76.2%) and 10 females (23.8%), with a mean age of 37.47±10.87 years. Postmortem analyses revealed frequent co-occurrence of tricyclic antidepressants and benzodiazepines in the samples. A notable 14.3% exhibited a history of underlying diseases, while 38.1% had documented psychological disorders. Methamphetamine was the predominant form of the drug, with an average dosage of 3428.7±1618.34 mg. Autopsy findings indicated pulmonary damage in 42.85%, cardiac damage in 23.8%, cerebral damage in 14.28%, hepatic damage in 28.6%, and renal damage in 9.52% of the deceased.

Conclusion: Our investigation revealed that amphetamine abuse typically culminates in swift mortality attributed to multi-organ compromise. Amphetamine induces adverse effects encompassing hepatic damage, rhabdomyolysis, pulmonary edema, cerebral edema, and cerebral hemorrhage.

Keywords: Amphetamine, Drug overdose, Postmortem toxicology, Autopsy, Forensic pathology, Forensic toxicology

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Introduction

The rising rates of substance abuse have become a significant public health concern in modern communities. The World Health Organization (WHO) has clearly emphasized the seriousness of this issue, recognizing it as one of the major challenges facing societies worldwide. In particular, drug overdoses have become the leading cause of injury-related deaths, highlighting the serious link between substance misuse and negative health effects(1). In 2017, the number of overdose-related deaths in the United States exceeded 70 200 (2). Amphetamines, such as methamphetamine and its derivative MDMA (3,4-methylenedioxymethamphetamine), are a class of substances commonly abused worldwide scale(3). In the past, amphetamines were used to treat a range of medical issues, including bedwetting, depression, Parkinson's

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Implication for health policy/practice/research/ medical education

This study highlights the urgent need for policies to regulate amphetamines and enhance surveillance of drug-related fatalities. Clinicians and forensic experts should be trained to identify and manage amphetamine toxicity. Further research is essential to standardize autopsy protocols for amphetamine-related deaths.

disease, attention deficit hyperactivity disorder (ADHD), coma, and alcoholism. However, today's medical practice has limited their use to certain specific conditions, primarily ADHD, narcolepsy, and short-term weight loss (4).

Methamphetamine produces a range of physical and psychological effects, such as increased arousal, euphoria, reduced fatigue, faster heart rate, and improved mood, dilated pupils, higher blood pressure, elevated body temperature, behavioral disinhibition, decreased appetite, increased alertness, and also heightened energy levels when taken at low to moderate doses. In contrast, higher doses or increased plasma levels of methamphetamine lead to a different set of effects, including extreme euphoria, high blood pressure, aggressive behavior, paranoia, rapid or incoherent speech, a fast pulse, anxiety, excessive sweating, and motor restlessness (5).

In the United States, overdose deaths related to psychostimulants with potential for abuse—primarily methamphetamine, excluding cocaine—have significantly increased over the past decade. This rise was especially evident from 2016 to 2019, with the rate jumping from 2.4 to 5.0 per 100 000 people (6). Additionally, provisional mortality data indicate that the estimated national total of overdose deaths linked to psychostimulants rose by 46%, from 16 011 between November 2018 and October 2019 to 23 352 from November 2019 to October 2020 (7). In 2021, there were 107 deaths related to amphetamine use in England and Wales, showing a clear upward trend in these fatalities (7).

The landscape of substance abuse is constantly changing around the world, and in Iran, there has been a significant shift in the main substances being abused. Traditionally, opioids like opium and heroin were the most common until 2008, when amphetamines became the primary substance of abuse (8). Importantly, among self-poisoning suicide deaths reported to the Tehran Legal Medicine Organization from 2011 to 2015, about 3% of these cases involved methamphetamine (9).

While select studies have explored the impact of amphetamine poisoning on patients, a notable gap persists in the literature concerning specific investigations into fatalities resulting from amphetamine intoxication across diverse age groups, based on forensic medical evidence. This research is prompted by the escalating trend in amphetamine abuse and the conspicuous absence of comprehensive studies addressing autopsy and pathology outcomes associated with amphetamine poisoning. As such, our study aims to scrutinize demographic variables, clinical manifestations, and the autopsy and pathological findings related to amphetamine intoxication over the course of a decade.

Objectives

This study aims to investigate and compare the autopsy and pathological findings in cases of amphetamine-related fatalities. It seeks to provide insights into the toxicological, clinical, and pathological profiles of these cases in Isfahan, Iran, over a decade (2012–2022), contributing to a better understanding of the impacts of amphetamine intoxication.

Materials and Methods

Study design

This cross-sectional study transpired between April 2012 and November 2022 within the clinical toxicology department of Noor hospital, a prominent referral institution situated in Isfahan province, Iran. Notably, our facility is purposefully equipped, staffed, and structured to cater exclusively to individuals afflicted by poisoning incidents. The study's inclusion criteria encompassed individuals who succumbed to amphetamine poisoning within this designated timeframe at our center, with their pertinent medical records archived at Khurshid Hospital. Deceased individuals whose bodies were transferred to the Forensic Medicine Organization of Isfahan for evaluation constituted the primary focus. Exclusion criteria involved cases wherein legal restrictions impeded access to the medical records of the deceased or when missing data exceeded 25% of the patient file information.

A comprehensive list of deceased individuals diagnosed with amphetamine poisoning was compiled by consulting the archive unit of Noor and Ali Asghar hospital through the center's information bank. Subsequently, medical records were procured from both hospital archives and the forensic medicine organization, and requisite information was extracted for analysis.

Statistical analysis

The extracted data encompassed demographic attributes (including age, gender, and marital status, history of somatic or psychiatric disease, addiction, and co-ingestion), cause of death, time elapsed between poisoning and death, route and also type of poisoning, necessity for intubation and ventilation, duration of hospitalization, internal organ damage, toxicology reports, across with autopsy and pathology results. Each patient's information was meticulously recorded in a checklist. The entirety of the collected data was input into SPSS software (version 26, IBM Corporation, Armonk, NY) for analysis. Qualitative data were reported using the mean ± standard deviation criterion. Differences between variables across distinct age groups were explored through Independent t-test, $\chi 2$,

ANOVA, and Fisher's exact tests in the final examination. A significance level of $P < 0.05$ was deemed statistically significant.

Results

This investigation scrutinized information pertaining to 42 individuals who succumbed to amphetamine poisoning. The demographic and clinical particulars of the deceased, comprising 32 males (76.2%) and 10 females (23.8%), were meticulously extracted for analysis. The mean age of the cohort was 33.09 ± 12.27 years, within a range of 18 to 67 years. Notably, intentional intoxication for the purpose of suicide emerged as the predominant mode of poisoning, accounting for 71.42% of cases across both genders. Furthermore, a substantial proportion, representing 66.7% of all patients, exhibited a positive history of addiction (Table 1). A discernible distribution in the route of drug administration was observed among the deceased, with 52.4% having orally consumed the substance and 47.6% opting for inhalation as the mode of ingestion. Additionally, 14.3% of the individuals exhibited a pre-existing medical condition, while 38.1% had a documented history of psychological disorders. The predominant form of the drug under scrutiny was methamphetamine, colloquially known as "Shishe" in Iran, with dosages spanning between 1000 and 6000 mg, and an average of 3428.57 ± 1618.34 mg. Investigations into fatalities revealed instances of two or more drug categories being implicated in 28 cases (66.7%). Remarkably, the most frequently co-ingested drugs were benzodiazepines and antidepressants (33.3%), followed by narcotics (28.6%) and alcohol (4.8%). A gender-based analysis indicated a significantly higher average incidence of co-ingestion of methamphetamine and opioids in males compared to

Table 1. Demographic findings and admission vital sign in deceased with amphetamine poisoning

Variables	Value
Gender	
Male	32 (76.2%)
Female	10 (23.8%)
Route of poisoning	
Ingestion	22 (52.4%)
Inhalation	20 (47.6%)
Type of exposure	
Suicide	2 (571%)
Drug overdose	10 (23.8%)
Unknown	2 (4.8%)
Addiction history	28 (66.7%)
History of psychological disease	16 (38.1%)
Underlying disease	6 (14.3%)
Co-ingestion	28 (66.7%)
Narcotics	12 (28.6%)
Benzodiazepines/Antidepressant	14 (33.3%)
Alcohol	2 (4.8%)
Age (y)	33.09 ± 12.27 (18-67)
Respiratory rate (/min)	18.82 ± 10.29/min (3-42)
Systolic blood pressure (mm Hg)	110.66 ± 37.50 mm Hg (60-180)
Diastolic blood pressure (mm Hg)	65.81 ± 21.39 mm Hg (30-110)
Heart rate (/min)	118.88 ± 42.71 bpm (30-185)
Temperature (°C)	37 ± 0.87 °C (36-39.5)
The time between amphetamine intake and admission (h)	2.19 ± 1.10 h(1-5)
The time between amphetamine intake and death (h)	17.05 ± 56.57 h(1-144)
Dosage	3428.57 ± 1618.34 mg (1000- 6000)
O_2 saturation	79.7059 ± 21.87% (30-98)

Where applicable, the results are presented as number (percent) or mean ± standard deviation (minimum-maximum).

Table 2. Clinical findings and treatment modalities of deceased with amphetamine intoxication on admission time in Isfahan, Iran (2012-2022)

Signs and symptoms	No. (%)
CNS depression	40(95.2%)
Coma/stupor	30 (71.4%)
Irritability	8 (19%)
Somnolent	2 (4.8%)
CNS depression, Seizures	8 (14.3%)
Vomiting	2 (4.8%)
Sweating	4 (9.5%)
Hyperthermia	12 (28.5%)
Hypertension	12 (28.5%)
Agitation	8 (19%)
Abdominal pain	4 (9.5%)
Pupil size	
Miosis	10 (23.8%)
Mydriasis	26 (61.9%)
Normal size	6 (14.3%)
Missing	0 (0%)
Abnormal lung auscultation	14 (33.3%)
Crackle	4 (9.5%)
Diminished	10 (23.8%)
Abnormal brain CT finding	6 (14.3%)
Tachycardia	20 (47.6%)
Bradycardia	4 (9.5%)
ECG changes	30 (71.4%)
Tachypnea	12 (28.5%)
Bradypnea	8 (19%)
Treatment protocol	**No. (%)**
Charcoal	16 (38.1%)
Laxative	20 (47.6%)
naloxone	28 (66.6%)
Gastric Lavage	16 (38.1%)
diazepam	4 (9.5%)
midazolam	18 (42.8%)
Intubation and mechanical ventilation	28 (66.6%)

females ($P<0.05$). The mean duration of hospitalization was 17.05 ± 56.57 hours, ranging from one to 144 hours. Pulse rates exhibited a wide range of 30 to 185 bpm, with an average of 118.88±42.71 bpm. Oxygen saturation levels upon admission of poisoned patients ranged from 30% to 98%, with an average of 79.7059 ± 21.87% (Table 1).

Clinical findings

The principal clinical presentations encompassed hypertension, agitation, central nervous system (CNS) depression, seizures, vomiting, sweating, abdominal pain, and diarrhea. Significantly, mydriasis was the predominant pupil size alteration observed in 61.9% of hospitalized patients. Electrocardiogram (ECG) changes manifested in 71.4% of patients during their hospital stay, and 19.04% of patients succumbed to sudden cardiac death. Furthermore, three cases exhibited alterations in brain CT scans (Table 2).

Treatment protocol

Patients underwent diverse therapeutic interventions, including the administration of activated charcoal (38.1%), the use of laxatives (42.9%), gastric lavage (38.1%), and naloxone (33.3%), and also intubation (66.7%), midazolam (42.85%), along with diazepam (2 patients). Additionally, hemodialysis was employed in one patient (Table 2).

Laboratory findings

The preliminary biochemistry findings are detailed in Table 3. Throughout the hospitalization period, liver failure affected 28.6% of patients, kidney failure was observed in 23.8%, aspiration pneumonia afflicted 66.7%, and sepsis was documented in only one case.

The autopsy findings

Amphetamine inflicted damage to various organs, affecting the lungs in 42.85% of cases, the heart in 23.8%, the brain in 14.28%, the liver in 28.6%, and the kidneys in 9.52% of the deceased (Table 4).

Discussion

This is a novel Iranian study that provides data on amphetamine-associated deaths from a forensic toxicology perspective. In this study, the demographic, clinical, laboratory, autopsy, and pathological findings of deaths due to amphetamine poisoning have been collected, which is unique in this regard. In our investigation at the forensic medicine center of Isfahan between 2012 and 2022, the mean age of the decedents was 33.09 ± 12.27

Table 3. Laboratory findings in amphetamine-intoxicated patients on admission time

	Mean	Standard Deviation	Minimum	Maximum
BUN (mg/dL)	22.28	20.27	9.00	94.00
Cr (mg/dL)	1.90	1.44	.70	6.30
BS (mg/dL)	162.81	89.20	60.00	351.00
WBC (/µL)	15800	7647.22	5800.00	34700.00
PMN (%)	73.62%	16.18%	46.80%	92.40%
HB (g/dL)	13.99	2.06	10.00	16.90
HCT (%)	42.66	5.62	33.20	52.70
PLT (/µL)	214835.8	103018.4	209.00	379000.0
Na (mEq/L)	138.26	5.51	128.00	150.00
K (mEq/L)	4.9	.92	3.50	6.70
PT (s)	15.69	5.21	10.60	29.00
PTT (s)	36.88	16.94	23.00	90.00
INR	1.35	.31	1.00	2.01
AST (U/L)	467.40	928.66	15.00	3521.00
ALT (U/L)	513.18	910.09	10.00	2560.00
Amylase (U/L)	896.00		896.00	896.00
Lipase (U/L)	102.80		102.80	102.80
pH	7.21	.20	6.67	7.43
HCO3 (mEq/L)	18.90	5.14	9.30	25.70
BE	-8.36	8.46	-28.30	1.50
PCO_2 (mm Hg)	49.44	18.63	21.30	89.20
PaO_2 (mm Hg)	40.59	24.31	15.80	86.80
CPK (U/L)	10665.35	19393.64	176.00	69910.00
LDH (U/L)	3464.92	3389.66	261.00	9770.00

BUN: Blood urea nitrogen, Cr: Creatinine, BS: Blood sugar, WBC: White blood cell count, PMN: Polymorphonuclear leukocyte, HB: Hemoglobin, HCT: Hematocrit, PLT: Platelet, Na: Sodium, K: Potassium, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio, AST: Aspartate transaminase, ALT: Alanine transaminase, CPK: Creatine phosphokinase, LDH: Lactate dehydrogenase.

Table 4. Summary of the autopsy and pathology finding

Organ	n	Gender	Addiction history	Co-ingestion	Average weight	Autopsy findings	Pathology findings
Brain	6	Male (4) Female (2)	66.6%	Alcohol		Cerebral edema and intracerebral hemorrhage	Degenerative changes in the number of cerebellar cells
Lung	20	Male (16) Female (4)	75%	Narcotics benzodiazepine	1568 g	Pulmonary edema, pneumonia and acute bronchopneumonia	Accumulation of red blood cells in the air alveoli and The sites of neutrophil infiltration in the lung parenchyma
Heart	8	Male (8) Female (0)	100%	Narcotics benzodiazepine	369.28 g	Dilated cardiomyopathy, cardiomegaly and accelerated atherosclerosis in coronary arteries	Myocyte fibrosis
Liver	8	Male (6) Female (2)	75%	Narcotics		Hepatic sub-massive necrosis and chronic hepatitis	Sinusoidal congestion of the liver lobular center and necrosis of hepatocytes and infiltration of lymphocyte inflammatory cells in the port space
Kidney	2	Male (2) Female (0)	75%	Narcotics Benzodiazepine		Acute kidney injury	Tissue tubular damage

years, and 76.2% of them were male. In a comparable study at the forensic medicine center of Tehran between 2011 and 2018, the mean age of the decedents was 37.47 ± 10.87 years, and 92.5% of them were male(10). Our findings diverge from those of Li et al who reported a nearly equal gender ratio for methamphetamine-related deaths in China (11). The present study reveals that methamphetamine use is more frequent among males in their second and third decades of life. This finding aligns with research conducted by Hadinezhad et al in 2017, which focused on methamphetamine users admitted to the emergency ward of a northern Iranian hospital (12). A comparable study conducted in San Francisco examined the demographic, toxicologic, and pathologic features of methamphetamine-related fatalities. The average age of the deceased was similar to that in the current study, and over 85% of the individuals were male (13).

In 71.42% of the deceased, amphetamine use was intentional, which contrasts with the findings of Darke et al, who reported that methamphetamine-related deaths were more frequently unintentional (14).

In our study, the most prevalent causes of death related to amphetamine poisoning included cardiac arrest and arrhythmia, respiratory arrest, overdose from multidrug use, and brain death due to intracerebral hemorrhage. These findings align with other literature, which indicates that in cases involving methamphetamine, decedents frequently succumbed to accidental overdoses linked to multidrug use (15). Additionally, many fatalities were associated with cardiac events, suicides, and intracerebral hemorrhage. Another study suggests that cardiovascular and cerebrovascular strokes should be regarded as primary or contributing factors in sudden deaths associated with methamphetamine use (16).

In our study, 66.7% of cases had a documented history of addiction to various substances, including methamphetamine, opioids, and benzodiazepines. Similarly, in another study, most patients had a recorded history of addiction to substances such as methamphetamine, opioids, and benzodiazepines for five years (449 cases, 32.33%). For other cases, the addiction duration ranged from 6–10 years (180 cases, 12.96%) or exceeded ten years (144 cases, 10.37%). The addiction history for the remaining cases was unknown(10).

In 66.7% of cases, deaths involving two or more categories of drugs were analyzed. Males showed a significantly higher average co-ingestion of methamphetamine and opioids compared to females ($P < 0.05$). A similar study also found that the most frequently identified substances, alongside methamphetamine, included both legal and illegal opioids (such as heroin metabolites like morphine), tramadol, methadone, tricyclic antidepressants, and benzodiazepines (10).

In our study, tachycardia was observed in 26 cases. Kirkpatrick et al conducted a comparison of the effects of methamphetamine and MDMA within the same individuals, finding that both substances produced similar effects in terms of heightened stimulation and cardiovascular activity (17).

Hypertension was another prevalent symptom observed in 12 cases. A related study noted that methamphetamine-induced hypertension has been linked to hemorrhagic cerebrovascular accidents (strokes), and the elevated levels of dopamine resulting from methamphetamine use may also play a role in neurobiological damage (18).

Laboratory data analysis revealed significant increases in creatine phosphokinase (CPK) and LDH levels. Additionally, an animal study found that ubiquitin and CPK levels rose in the renal tubules of rats injected with methamphetamine, suggesting that methamphetamine-related rhabdomyolysis may lead to renal tubular damage(19). Volkow et al reported that methamphetamine was most concentrated in the lungs (22%), liver (23%), brain (10%), and kidneys (7%) (20). Our data suggest that pulmonary edema and pneumonia was the most repetitive finding. These reports were confirmed in the following

studies. Karch et al found that pulmonary edema was present in 70% of methamphetamine-related fatalities, pneumonia occurred in 8%, and emphysema was observed in 5%. Additionally, 11% of autopsies revealed birefringent crystals, which could potentially contribute to granuloma formation and fibrosis (13). It seems that one of the reasons for pulmonary edema is excessive hydration of the patient due to the management of rhabdomyolysis. Additionally, Tsai et al concluded that methamphetamine abuse is associated with increased rates of pneumonia and acute respiratory failure in both men and women. However, acute exacerbations of chronic obstructive pulmonary disease were more frequently observed in women. No association was found between methamphetamine use and acute asthma (21). Fifteen patients experienced cardiovascular issues during hospitalization, consistent with findings from a similar study indicating that cardiovascular disease is common among methamphetamine users due to the drug's interaction with L-type calcium channels in cardiomyocytes (22). We found that cardiomegaly and atherosclerosis in coronary arteries are common in amphetamine deceased. Wijetunga et al and Yeo illustrate methamphetamine use may cause cardiomyopathy in some users (23, 24). Related research has shown that methamphetamine abuse is associated with various cardiovascular issues, including accelerated atherosclerosis, which can lead to myocardial infarction at a relatively young age (25). Additionally, Broadley et al found that amphetamines can induce vasoconstriction independently of adrenoreceptors, neuronal transport mechanisms, or serotonin receptors (26). A prior study on methamphetamine's impact on the cardiovascular system demonstrated a strong association between methamphetamine abuse and cardiovascular pathology (27). A study conducted in Texas by Westover et al reveals a modest but significant correlation between amphetamine abuse and acute myocardial infarction. The authors describe the pharmacodynamic and pathophysiological mechanisms involved, which include coronary artery vasospasm, catecholamine-induced platelet aggregation, atherosclerotic plaque rupture, myocardial necrosis, and increased myocardial oxygen demand (28). Our study indicates that cerebral edema and intracerebral hemorrhage are more pronounced in fatalities, a finding supported by previous research. It appears that patient overhydration significantly contributed to the observed cerebral edema, and earlier study have reported necrotizing vasculitis linked to intracerebral hemorrhage in methamphetamine users (16). Two additional studies found a high risk of ischemic stroke and cerebral hemorrhage among methamphetamine users (29, 30), while another study identified an increased risk of cerebrovascular conditions among users of both amphetamines and cocaine(31). In our investigation, we observed hepatic sub-massive necrosis and chronic hepatitis. Similarly, a study by Karch et al found that methamphetamine abuse leads to liver damage, with 15.4% of cases exhibiting hepatic steatosis, 9% cirrhosis, 6% portal hypertension, and 5% hepatitis(22). An examination of kidney tissue revealed tubular damage, and a similar study found that nephrosclerotic lesions are also prevalent among stimulant users (32).

Conclusion

To our knowledge, this is the first forensic-based epidemiologic study of amphetamine deceased to investigate clinical manifestation and pathology findings with amphetamine abuse. The findings indicate a modest association between amphetamine abuse and pulmonary cerebral and edema and atherosclerosis and rhabdomyolysis. Death caused by amphetamine is usually rapid and results from multi-organ damage.

Limitations of the study

The autopsy and pathological findings from the Legal Medicine Organization in Isfahan, Iran, show substantial gaps in data.

Authors' contribution

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Writing–review & editing: Mahmood Tabandeh, Maedeh Barahimi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical considerations adhered to the principles outlined in the 1975 Declaration of Helsinki, as revised in 1983. The study was conducted under the auspices of the Legal Medicine Research Center, Legal Medicine Organization, Isfahan, Iran, and received approval from the Clinical Toxicology Department of Isfahan University of Medical Sciences under registration number (Ethical code#IR.MUI.MED.REC.1400.473), with additional approval granted by the Institutional Ethics Committee under Research Project 820246. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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