Original Article

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The Study of Pathological Findings in Medico-Legal Cases Positive for Urinary Methamphetamine in Thai Postmortem Cases

Peerayuht Phuangphung MD, PhD[1], Wichai Wongchanapai MD, PhD[1]

[1] *Department of Forensic Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand*

ABSTRACT

OBJECTIVE: This study aims to study pathological findings in Thai postmortem cases who were positive for methamphetamine in urine and compare these findings to the control group which was negative for drugs of abuse.

METHODS: Retrospective study was conducted from autopsy reports and toxicological data of Thai postmortem cases between January 2018 and March 2020. The data were categorized into two groups including methamphetamine group and control group based on the detection of methamphetamine in urine. Sex, age and pathological findings were recorded in both groups. Chi-square test, Mann-Whitney U test and multiple comparisons with Games-Howell post-hoc test were performed where appropriate.

RESULTS: There were 85 methamphetamine cases with 170 in the negative control group. All study subjects were male. Average ages of these two groups were 46.71 and 45.38 years old. Heart weight in the methamphetamine group was significantly greater than in the control group ($p<0.05$). Histologically, the methamphetamine group showed significant myocardial hypertrophy and interstitial fibrosis compared with the control group ($p<0.01$). The presence of alveolar hemosiderin-laden macrophages in the methamphetamine group was significantly higher than in the control group ($p<0.001$). Coronary artery stenosis was considered adjusted with age. In the methamphetamine group, the stenosis of the left anterior descending artery (LAD) at greater than 50% was significantly detected in younger ages than in the control group ($p<0.05$).

CONCLUSION: Methamphetamine had an association with increased heart weight and LAD stenosis greater than 50% in younger age in Thai male cadavers.

KEYWORDS: coronary artery, heart, methamphetamine, Thai

INTRODUCTION

Methamphetamine is an amphetamine-type stimulant and the most prevalent drug found in Thailand. The United Nations Office on Drugs and Crime (UNODC) Report in 2019, listed Thailand in the top five countries where the highest amount of methamphetamine was seized[1]. Worasuwannarak et al. reported that methamphetamine was the most common drug detected in Thai medico-legal postmortem cases at 6.37% in 2018 and the trend was increasing compared to other drugs[2]. Thus, the impact of methamphetamine abuse on the physical and mental health of Thai people is also possibly increasing.

Methamphetamine has several negative effects on multiple organ systems, particularly the cardiovascular and central nervous systems.

Corresponding Author: Peerayuht Phuangphung
E-mail: peerayuht.phu@mahidol.ac.th
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Previous studies detected cardiovascular system defects such as coronary atherosclerosis and cardiomegaly as a result of long-term methamphetamine abuse[3-6]. The prevalence of stroke in the young also increased in methamphetamine abusers[7-8]. However, these studies involved people from European countries, Australia and the United States of America (USA) and applying these findings to Thai people may be erroneous. Prasobsrikul et al. reported pathological findings in 61 Thai postmortem cases where methamphetamine was detected in biological samples submitted for toxicological analysis[9]. However, this study mainly focused on the analysis of blood methamphetamine concentrations and did not compare the pathological findings to a control Thai population group where methamphetamine was not detected.

To rectify this research lacuna, this study aims to compare pathological findings of Thai postmortem cases that were positive for only methamphetamine and amphetamine as its metabolite in urine to those that were negative for drugs of abuse to obtain data on the effect of methamphetamine abuse on the principal organ systems in the Thai population. Findings will be useful for interpretation of pathological findings in the Thai population and raise awareness when methamphetamine abuse is suspected in Thai medico-legal cases.

METHODS

A retrospective case control study was conducted from autopsy reports and toxicological data of Thai postmortem cases sent for medico-legal autopsy at the Department of Forensic Medicine, Faculty of Medicine Siriraj Hospital from 1st January 2018 to 31st March 2020. Inclusion criteria included Thai people who were 18 years old and over, for whom urine samples could be collected. Definite causes of death were identified by gross and microscopic findings for all the studied cases. The Thai postmortem cases were divided into two groups

1. Methamphetamine group: urine samples detected for only methamphetamine and amphetamine. Due to definition, there were only male subjects in the methamphetamine group.

2. Control group: urine samples were not positive for any drugs of abuse and medications as described below. The control group was recruited from Thai male subjects in the same period of the methamphetamine group for consistency with male subjects in the methamphetamine group.

The urine samples were analyzed by a liquid chromatography-tandem quadrupole Time-of-Flight mass spectrometry (LC-QTOF) for targeted drugs of abuse including methamphetamine, amphetamine, 3,4-methylenedioxy-methamphetamine (MDMA), 3,4-methylenedioxy-amphetamine (MDA), 3,4-methylenedioxy–N-ethyl-amphetamine (MDEA), methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), buprenorphine, fentanyl, tramadol, ketamine, diazepam, desmethyldiazepem (nordiazepam), oxazepam, temazepam, lorazepam, alprazolam, clonazepam, midazolam, chlordiazepoxide, phenazepam, amitriptyline, nortriptyline, fluoxetine, sertraline, chlorpromazine, haloperidol, and mitragynine. Urine samples were also analyzed by a gas chromatography mass spectrometry (GC-MS) for 6-acetylmorphine (6-AM), morphine, codeine, cocaine, benzoylecgonine, delta-9-tetrahydro-cannabinol (THC), and 11-nor-9-carboxy- delta-9-tetrahydrocannabinol (THC-COOH). Urine samples in the control group were negative for all drugs of abuse and medications as described above.

Exclusion criteria included decomposed bodies whose organ pathologies could not be evaluated, dead bodies who had underlying diseases that impacted organ pathologies like diabetes mellitus, hypertension and ischemic heart disease, dead bodies with drug intoxication, and dead bodies who had cardiac injuries that led to inaccurate evaluation of heart weights. Data including sex, age, height, weight, and cause of

death were recorded in each group. Body mass index (BMI) was calculated from height and weight. Pathological findings in each group were documented including:

1. Heart: heart weight, left ventricular thickness, degree of coronary artery stenosis for each coronary vessel (left anterior descending artery (LAD), right coronary artery (RCA) and left circumflex artery (LCX)), presence of microscopic myocardial hypertrophy and presence of interstitial myocardial fibrosis.

Degree of coronary artery was stratified into 4 categories by histological findings: no stenosis, mild stenosis (<50%), moderate stenosis (50-75%) and severe stenosis (≥75%).

2. Brain: presence of atherosclerosis of either anterior or posterior circulation of circle of Willis including intracranial internal carotid arteries, middle cerebral arteries, basilar artery and vertebral arteries, and presence of areas of cerebral infarction or intracerebral hemorrhage.

3. Lungs: presence of pathological signs of pulmonary hypertension including proliferation of medial layer of pulmonary vessels with obliterated lumen or plexogenic pulmonary arteriopathy, and presence of alveolar hemosiderin-laden macrophage (heart-failure cell).

4. Liver: presence of triaditis (accumulation of chronic inflammatory cells at portal triad) Analysis of methamphetamine in urine.

Urinary methamphetamine and amphetamine concentrations were quantified by a gas chromatography nitrogen phosphorus detector (GC-NPD). Urine samples were extracted by liquid-liquid extraction protocol. Briefly, 50 µL of 25 µg/mL phentermine (internal standard) was pipetted into a test tube and 1 mL of urine was added. 50 µL of 25 µg/mL sodium hydroxide was pipetted into the test tube for basic pH adjustment. Then, 5 mL of dichloromethane was pipetted into the test tube. The test tube was shaken for 15 minutes and then centrifuged at 4,000 rpm for 10 minutes. The lower layer was taken and 50 µL of 25% hydrochloric acid in methanol was added. This solution was evaporated for dryness using a nitrogen evaporator at room temperature. Then, 50 µL of methanol was used for re-constitution and 2 µL was injected into the GC-NPD.

Method validation was performed in accordance with SWGTOX 2013 guidelines[10]. Selectivity and interference studies were performed to ascertain no interference peaks occurring at retention times of amphetamine, phentermine and methamphetamine at 4, 5 and 6 minutes, respectively. Limit of detection (LOD) and lower limit of quantitation (LLOQ) were determined by spiking gradually decreasing concentrations of amphetamine and methamphetamine working solutions into blank postmortem urine. Amphetamine and methamphetamine at 150 ng/mL and 250 ng/mL produced peaks with a signal-to-noise ratio (S/N) greater than 3 times and 10 times, respectively. Thus, 150 ng/mL and 250 ng/mL were set as LOD and LLOQ for both amphetamine and methamphetamine, respectively.

A calibration model was performed using six amphetamine and methamphetamine calibrators ranging from 250 to 10,000 ng/mL (250, 500, 1,000, 2,500, 5,000 and 10,000 ng/mL). Calibration curves were generated using Agilent Software® Version 6.20 from back-calculated concentrations for each calibrator. Curve weighting factors 1/x were used to obtain the best linear regression fit that achieved r^2 ≥ 0.99 and accuracy of each calibrator within ±15% (for LLOQ within ±20%). Three spiked QC samples at 750, 1,500 and 7,500 ng/mL of amphetamine and methamphetamine were analyzed to determine accuracy and precision. Accuracy and intra-day and inter-day precision for each QC were within acceptable criteria at ±15% accuracy and ±15% coefficient of variation (%CV). There was no carry over following the injection of spiked blank urine samples with amphetamine and methamphetamine at 50,000 ng/mL. Extract stability of three QC samples

was evaluated for auto-sampler stability and stability in the fridge (4 °C). Amphetamine and methamphetamine were stable in the extract samples for both in the auto-sampler and in the fridge (4 °C) after 72 hours and 5 days, respectively.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS for Window version 21. Descriptive statistics were analyzed for mean, median, range and standard deviation. Continuous data were tested using the Kolmogorov-Smirnov test and Levene's test for equality of variance. Age and BMI were both normally distributed; therefore, the independent sample t-test was used to compare age and BMI between the methamphetamine and the control groups. Heart weight data were not normally distributed, and the Mann-Whitney U test was employed for data comparison. Multiple comparisons were assessed using the Games-Howell post-hoc test to analyze the degree of coronary artery stenosis between age groups. Other binary data were analyzed using non-parametric contingency table Chi-square test. Statistical significance was set at p-value <0.05.

This research project was approved by the Institute Review Board of the Faculty of Medicine, Siriraj Hospital, Mahidol University (COA No. Si 414/2020 and Research Project No.356/2563 (IRB4)).

RESULTS

A total of 85 cases were positive for methamphetamine in urine and 170 control cases were negative for drugs of abuse. All the subjects were male. The age and BMI profiles of these two groups were shown in Table 1. These profiles were not significantly different. The comparison of causes of death between these two groups was shown in Table 2. The figure of traffic accident in the methamphetamine group were significantly less than the control group whereas the figure of hanging in the methamphetamine group were significantly greater than the control group (p<0.001). However, there was no statistical significance for the number of other causes of death between these two groups.

Table 1 Age and BMI profiles of the methamphetamine and the control groups

Parameters	Methamphetamine group		Control group		P-value
	Mean ± SD	Range	Mean ± SD	Range	
Age (years)	36.56 ± 9.62	22-65	37.60 ± 10.94	20-65	>0.05
BMI (kg/m^2)	23.12 ± 3.76	17.44-31.31	23.07 ± 3.15	17.27-33.06	>0.05

Abbreviations: kg, kilogram; m, meter; SD, standard deviation

Table 2 Comparison of causes of death between the methamphetamine and the control groups

Cause of death	Methamphetamine group	Control group	P-value
Traffic accident	16/85 (18.82%)	88/170 (51.76%)	<0.01
Hanging	30/85 (35.29%)	20/170 (11.76%)	<0.01
Coronary artery disease/acute myocardial infarction	19/85 (22.35%)	28/170 (16.47%)	>0.05
Intracerebral hemorrhage	5/85 (5.88%)	8/170 (4.71%)	>0.05
Electrocution	6/85 (7.06%)	5/170 (2.94%)	>0.05
Ruptured aortic dissection	2/85 (2.35%)	5/170 (2.94%)	>0.05
Pneumonia	3/85 (3.53%)	6/170 (3.53%)	>0.05
Drowning	2/85 (2.35%)	6/170 (3.53%)	>0.05
Gunshot wound to the head	2/85 (2.35%)	4/170 (2.35%)	>0.05

The top three causes of death in these two groups were hanging, traffic accident, and coronary artery disease/acute myocardial infarction. Hanging recorded a higher percentage in the methamphetamine group (30/85, 35.29%) compared with the control group (20/150, 11.77%) whereas traffic accident was predominant in the control group (88/170, 51.76%) compared with the methamphetamine group (16/85, 18.82%). Coronary artery disease/acute myocardial infarction and cerebrovascular disease comprised 22.35% (19/85) and 5.88% (5/85), whereas ruptured aortic dissection presented only 2.35% (2/85) among all causes of death in the methamphetamine group.

Heart weight in the methamphetamine group was significantly higher than in the control group as shown in Table 3 (p=0.043). However, a comparison of left ventricular thickness values between these two groups showed no statistical significance.

For microscopic findings, myocardial hypertrophy and interstitial fibrosis were significantly higher in the methamphetamine group than in the control group (p<0.001 and p=0.007) as shown in Table 4.

When degree of coronary artery stenosis was considered, there were 16.5% (14/85), 11.8% (10/85) and 10.6% (9/85) of moderate stenosis for LAD, RCA and LCX and there were 14.1% (12/85), 9.4% (8/85) and 1.1% (1/85) of severe stenosis for LAD, RCA and LCX, respectively. When the number of coronary artery stenosis was considered, severe single vessel disease, double vessel disease and triple vessel disease comprised 11.8% (10/85), 4.7% (4/85) and 1.1% (1/85), respectively. Thus, there were 17.6% (15/85) for overall severe coronary artery stenosis.

Table 3 Comparison of gross cardiac parameters between the methamphetamine and the control groups

Cardiac parameters	Methamphetamine group		Control group		P-value
	Mean ± SD	Range	Mean ± SD	Range	
Heart weight (g)	356.59 ± 103.63	200-680	326.53 ± 62.50	220-670	0.043
Left ventricular thickness (cm)	1.34 ± 0.18	1.0-1.9	1.32 ± 0.16	1.1-2.0	>0.05

Abbreviations: cm, centimeter; g, gram; SD, standard deviation

Table 4 Comparison of histologic cardiac parameters between the methamphetamine and the control groups

Cardiac parameters		Methamphetamine group	Control group	P-value
Myocardial hypertrophy	Presence	40	42	<0.001
	Absence	45	128	
Interstitial fibrosis	Presence	24	24	0.007
	Absence	61	146	

Degree of stenosis at greater than 50% in each coronary vessel was used to compare results between these two groups. Multiple comparisons were assessed using the Games-Howell post-hoc test to analyze the degree of coronary artery stenosis between age groups, The LAD with degree of stenosis greater than 50% was detected at a younger age in the methamphetamine group and significantly higher than in the control group (p=0.041) as shown in Table 5. However, no significant difference was found between the degree of stenosis and age group for the right coronary artery (RCA) and left circumflex artery (LCX) between these two groups (p>0.05).

When other autopsy parameters were analyzed, the presence of hemosiderin-laden macrophages (heart-failure cells) in lungs was the only parameter that presented at a significantly higher rate in the methamphetamine group than

in the control group as shown in Table 6. Our results did not detect microscopic signs of pulmonary hypertension in any cases in the methamphetamine group.

When urinary methamphetamine and amphetamine concentrations were considered, the median concentration of methamphetamine was 4,403.76 ng/mL (range: 365.40-17,6158.18 ng/mL) whereas the median concentration of amphetamine was 547.64 ng/mL (range: <150-16,653.82 ng/mL). When urinary amphetamine concentrations greater than 250 ng/mL were considered, the median concentrations of methamphetamine and amphetamine were 5,062.34 ng/mL (range: 919.44-17,6158.18 ng/mL) and 671.98 ng/mL (range: 250.13-16,653.82 ng/mL), respectively. The mean and median amphetamine/methamphetamine percentage ratios were 16.57% and 13.86% (range: 3.79%-55.66%), respectively.

Table 5 Comparison of degree of coronary artery stenosis against age between the methamphetamine and the control groups

Coronary	Degree of stenosis	Age (years old)				P-value
		Methamphetamine group		Control group		
		Mean ± SD	Range	Mean ± SD	Range	
LAD	<50%	35.56 ± 9.13	22-61	33.81 ± 9.41	20-61	>0.05
	≥50%	38.85 ± 10.48	25-65	45.53 ± 9.63	24-65	0.041
RCA	<50%	34.81 ± 8.66	22-61	35.22 ± 9.72	20-61	>0.05
	≥50%	43.11 ± 10.42	25-65	48.29 ± 9.75	25-65	>0.05
LCX	<50%	35.23 ± 9.19	22-65	36.03 ± 10.37	20-65	>0.05
	≥50%	46.60 ± 6.57	35-56	48.18 ± 8.72	32-65	>0.05

Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; SD, standard deviation

Table 6 Association of other autopsy parameters between the methamphetamine and the control groups

Other associated paramete		Methamphetamine group	Control group	P-value
Atherosclerosis of circle of Willis	Presence	14	22	>0.05
	Absence	71	148	
Presence of intracerebral hemorrhage	Presence	5	8	>0.05
	Absence	80	162	
Presence of cerebral infarction	Presence	3	4	>0.05
	Absence	82	166	
Hemosiderin-laden macrophage in lungs	Presence	31	35	0.006
	Absence	54	135	
Triaditis in liver	Presence	27	55	>0.05
	Absence	58	115	

DISCUSSION

Methamphetamine was associated with negative effects on the cardiovascular system in the Thai population. Severe coronary artery stenosis (≥75%) comprised 17.6% and severe single vessel disease was the most common form in this study. LAD was the most common affected vessel both in moderate and severe stenosis. The incidence of severe coronary artery stenosis could be varied among literatures. Karch et al. stated that severe coronary atherosclerosis was found at 5.8% in all methamphetamine abusers[3]. However, Darke et al. indicated that severe coronary atherosclerosis (>75% occlusion) was found at 19.0% in methamphetamine-related cases[5]. The left main coronary artery and/or LAD were the most common vessels involved in coronary atherosclerosis in the methamphetamine group[5].

Our results showed that degree of LAD stenosis greater than 50% was detected in younger ages in the methamphetamine group than in the control group. This result supported that methamphetamine was associated with the increasing rate of coronary atherosclerosis. In addition, the methamphetamine group presented with higher heart weight than the control group. Microscopic findings showed that the methamphetamine group had a greater degree of interstitial myocardial fibrosis and myocardial hypertrophy than the control group. Previous studies showed that methamphetamine was associated with cardiotoxic effects and produced increased heart weight[3-6]. These findings were consistent with previous studies and supported that methamphetamine had an impact on cardiac function[3-6,9,11-12]. Increased catecholamine release, increased reactive oxygen species, cellular organelle modification and promotion of inflammatory pathway were the other mechanisms identified for cardiac infrastructure alteration[11-12]. For atherogenicity, a previous study suggested that methamphetamine increased atherogenic cytokines and reactive oxygen species and promoted inflammatory T cells and macrophages[13]. This response enhanced atherogenicity and increased the rate of coronary atherosclerosis[13]. Our finding supported that methamphetamine was associated with coronary atherosclerosis in the younger age group, especially for LAD.

Other autopsy findings showed that increased alveolar hemosiderin-laden macrophages (heart-failure cells) were strongly associated with methamphetamine use when compared with the control group. A review publication stated that the stimulant like cocaine was associated with an increasing number of hemosiderin-laden macrophages in broncho-alveolar lavage compared to smokers and non-smokers and this finding suggested the association with chronic subclinical alveolar hemorrhage[14]. However, no evidence existed for the association between the presence of increased alveolar hemosiderin-laden macrophages and methamphetamine use. Our findings should be further studied for the cause of increased alveolar hemosiderin-laden macrophages in methamphetamine users. Atherosclerosis of the circle of Willis and triaditis recorded no association with the methamphetamine group. Previous studies indicated that intracranial atherosclerosis was strongly associated with increased age, hypertension and diabetes mellitus[15,16]. A review study suggested that methamphetamine-associated cerebrovascular disease was possibly associated with cerebral arteritis or vasospasm[17]. A previous study identified triaditis at 6.0% in the methamphetamine group but no statistical difference was recored between the methamphetamine group and the control group3. Our result concurred with this previous study, suggesting that triaditis might be related to other mechanisms such as viral infection, parasitic infestation, immune-mediated mechanism and alcohol. Unfortunately this study detected no histologic findings of pulmonary hypertension in the methamphetamine group. Subject gender was possibly associated with this finding because a previous study showed that female sex was associated with the presence of pulmonary arterial hypertension in documented methamphetamine abusers[18]. As all the study subjects were male, this might not show the effect of methamphetamine use on pulmonary vessels. Thus, further research should be conducted on Thai female methamphetamine abusers to prove the incidence of pulmonary arterial hypertension.

Our results showed that urinary methamphetamine and amphetamine concentration ranges in Thai people were relatively large. When compared with a previous study, urinary methamphetamine and amphetamine concentration ranges in methamphetamine-related deaths were 143-90,340 ng/mL and 36-39,300 ng/mL while median urinary methamphetamine and amphetamine concentrations were 5,300 ng/mL

and 1,400 ng/mL, respectively[19]. Our results showed a higher concentration range in methamphetamine and a lower concentration range in amphetamine compared with this study, possibly because of different purity, dosage, time and frequency of methamphetamine use by the subjects before death. Al-Asmari also found that the median amphetamine/methamphetamine percentage ratio in urine was 25%[19]. However, Kim et al. reported that mean amphetamine/methamphetamine percentage ratio in urine from volunteers under controlled oral methamphetamine administration ranged from 13.4 ± 6.5% to 22.7 ± 16.1%[20]. When compared with two studies on Thai people, Kaewpunya and Kaewmun found that mean urinary methamphetamine and amphetamine percentage ratios in Thai living people were 22-41% and 20-33%, respectively[21-22]. Our ratio results were lower than the ratios in these two previous studies on Thai people. This finding could be attributed to the difference between the time interval of methamphetamine use in our study and these two studies because the previous study suggested that urinary methamphetamine and a mphetamine percentage ratio varied over time after methamphetamine use[20].

This study had some limitations. First, all subjects were Thai males. These led to limitations when generalizing the findings to Thai females. Second, histories of methamphetamine abuse in the methamphetamine group including the duration and frequency of abuse, route of administration and forms of drugs used were not available. Therefore, association between these variables and cardiac parameters and degrees of coronary stenosis could not be assessed. Finally, only a small number of subjects presenting with degrees of coronary stensis for RCA and LCX at greater than 50% possibly led to reduced statistical significance for multiple comparisons for RCA and LCX. Thus, our findings should be viewed with caution and further studies should be conducted to expand and confirm our results.

CONCLUSION

Methamphetamine had an association with some pathological findings in Thai male subjects. Increased heart weight, myocardial hypertrophy and interstitial fibrosis were significantly found in methamphetamine positive cases. Methamphetamine positive cases with LAD stenosis greater than 50% also presented at a younger age than in the control group.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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None

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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