RISK OF METHAMPHETAMINE ABUSE PROMOTED CEREBRO-CARDIOVASCULAR DEFECTS IN THAI CADAVERS WHICH SENT TO AUTOPSY AT INSTITUTE OF FORENSIC MEDICINE, THAILAND

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ABSTRACT: Methamphetamine abuse has also been a social and public health problems especially in Thailand. Most of the studies in other countries suggest that using methamphetamine may be one of risk factors for cerebro-cardiovascular defects. To clarify this relationship in Thai people, the authors used a retrospective and 1:1 matched case-control as a tool for study. Samples were collected from cadavers that sent to autopsy at Institute of Forensic Medicine (IFM), Thailand in year 2008. Of 483 age and gender match pairs were evaluated for this association. Magnitude of risk described in odds ratio equal to 4 (±95% CI=1.13-14.17) and McNemar's chi-square test, p=0.035. This results indicated that methamphetamine abuse was associated with a 4 folds increasing in risk for cerebro-cardiovascular defects. This trend finding seemed to be a terrible problem that public authorities should be realized and rapid take action to control those risks. Furthermore, a truly reflection about this risk in alive Thai population should be performed using a prospective cohort design.

Keywords: Methamphetamine, cerebro-cardiovascular defects

INTRODUCTION: Using amphetamine type stimulants (ATS) has been a global problem, especially in Thailand. Report from the United Nations Office on Drugs and Crime (UNODC) indicated that in 2007, 84,073 ATS-related offences were arrested in Thailand, 97% for methamphetamine tablet related offences, 2% for crystalline methamphetamine and less than 1% for ecstasy related offences[1)]. Furthermore, the Office of the Narcotics Control Board (ONCB) national household survey in 2007 reported that approximately 1.7 % (788,948 peoples) of 12-65 years old Thai people had tried methamphetamine at least once in their life-time[2)]. Thus methamphetamine abuse is a major social and public health problem in this country.

Numerous medical science literatures such as animal studies, human case reports and an autopsy reports suggest a link between using methamphetamine and cerebro-cardio toxicity. Literatures have highlighted methamphetamine as a class of cardiac risk. Using methamphetamine can lead to a number of cardiovascular complications like arrhythmias, hypertension, acute coronary syndrome, stroke, etc.[3-5)] and sometimes resulting in cardiovascular collapse and death. It also related to ischemic and hemorrhagic cerebrovascular accident associated with the vasoconstrictive and hypertensive effects of methamphetamine[6)].

Several studies were concerned with regard to the mechanisms of methamphetamine induced cerebro-cardiovascular defects. Briefly, methamphetamine produces intoxication through potentiates the presynaptic neural terminal's release of catecholamine neurotransmitters, norepinephrine and dopamine, causing stimulation of the postsynaptic receptor and inhibits reuptake of these neurotransmitter. High levels of catecholamine are responsible for cardiotoxicity by coronary vasoconstriction, calcium overload, and the production of oxygen-free radicals by either the auto-oxidation of catecholamines or their degradation by monoamine oxygenase. Abnormal catecholamine levels also have some other detrimental effects on the heart, such as inducing hypertrophy, myocardial ischemia and reperfusion, fibrosis, infarction, and cardiomyopathy[7)] and also potently spasm of the cerebral arteries results in blood-vessel rupture, cerebral ischemia, and cerebral hemorrhage[8-10)]. Thus, high levels of catecholamine from using methamphetamine are a significant factor that leads to cerebro-cardiovascular defects.

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Autopsy report is one of valuable medical data. Institute of Forensic Medicine (IFM), Royal Thai Police Headquarter is responsible for the medico-legal examination. The cadavers with unclear causes and manners of death or unnatural death cases were sent here to autopsy by police investigators. Due to seriousness of methamphetamine induced complications, authors have attempted to study the relationship between using meth-amphetamine and prevalence of cerobro-cardio vascular defects in Thai cadavers which sent to autopsy at IFM.

Information from this study can lead to assessment risk of methamphetamine induced cerebro-cardiovascular defects and assist to push public health policy to prevent the serious complications of Thai methamphetamine users.

MATERIALS AND METHODS: A retrospective, individual matched case-control design was used for evaluating the relationship between meth-amphetamine abuse and cerebro-cardiovascular defects. Autopsy reports were obtained from Pathology division of IFM and toxicological reports were obtained from Toxicology division of IFM, from January 2008 to December 2008.

The inclusion criteria consisted of an unembalmed adult cadavers with unexplained cause of death by external examination (body was found dead unexpectedly at home, outdoors or in the hospital emergency room). The internal autopsy was followed by microscopic and toxicology examination. Cause of death was determined according to different pathological features, toxicology and circumstances. The exclusion criteria consisted of fatal external wounding, immersion death, asphyxia, poisoning and in decomposed bodies.

As for appropriate statistics technique and information from previous studies, gender and age might act as confounding factors for correctly interpretation data. Use of 1:1 individual matched case-control study and McNemar's chi-square analysis is a suitable technique that could be reduced improper effect. In this study, gender and age (±5 years) were used as the criteria of matching, which were matched by consecutive IFM number. After tabulating report data, the risk factors for cerebro-cardiovascular defects among matched case-control pairs were determined by using McNemar's test; the risk of methamphetamine induce cerebro-cardiovascular defects was given by the odds ratio (ÔR) calculated as the proportion of discordant pairs s/t), where s and t indicated the number of pairs with only the case (s) or only the control (t) exposed to a risk factor. The 95% confidence interval (CI) of the ÔR was then calculated with the aid of tables based on the binomial distribution. The sample size[11], N = 418 pairs, calculated from this formula $N = [Z_{\alpha}(\sqrt{2p}) + Z_{\beta}\sqrt{(2(p\text{-}+)(p+\text{-})/p)}]^2 / [(p\text{-}+) - (p+\text{-})]^2$ where N = total pairs, (p+-)= proportion of discordant pairs that the case was exposed to the risk factors but the control was not, (p-+) = proportion of discordant pairs with only the control exposed to a risk factor but the case was not, p=[(p+-)+(p-+)]/2. Because of no previous study design that using 1:1 matched case-control to evaluate that relationship, so in this study the authors set (p-+) approximated to 0.15 and (p+-) approximated to 0.07, Z_{α}; Z value at level of significance = $Z_{0.975}$ = 1.96 and Z_{β} ; Z value at power of test equal to 1-β ; $Z_{\beta} = Z_{0.95}$ = 1.64.

RESULTS: Frequency of gender difference and mean age of 483 pairs of matched case-control samples were shown in Table 1.

Table 1 Gender and age difference in matched case-control samples

	n	Gender		Age			
		Female (%)	Male (%)	Mean	S.D.	Median	Min- Max
Case	483	71(14.7%)	412(85.3%)	52.69	13.76	52.00	**19-94**
Control	483	71(14.7%)	412(85.3%)	46.61	13.99	44.00	**14-98**
Total	**966**	**142(14.7%)**	**824(85.3%)**	**49.65**	**14.20**	**48.00**	**14-98**

Table 2 Cause of death and urine methamphetamine test result of samples

Cause of death		Urine methamphetamine test		Total
		Positive	Negative	
Case	Cardiovascular disease	11 (2.8%)	384 (97.2%)	395
	Cerebrovascular disease	2 (2.3%)	86 (97.7%)	88
	Total	13 (2.7%)	470 (97.3%)	483
Control	Infective & other disease	1 (2.3%)	43 (97.7%)	44
	Undetermined cause of death	3 (0.7%)	436 (99.3%)	439
	Total	4 (0.8%)	479 (99.2%)	483

Table 3 McNemar's analysis report

		[Control] urine methamphetamine		
		Positive (+)	**Negative (-)**	**Total**
[Case] urine methamphetamine	**Positive (+)**	1 (++)	12 (+-) (s)	13
	Negative (-)	3 (-+) (t)	467 (--)	470
	Total	4	479	483

McNemar's Test Result : P = 0.035 (2 tailed) ÔR = 4.0 95% CI =1.13-14.17

Table 4 Autopsy and toxicology findings of methamphetamine positive samples

Case No.	Type	Sex /Age	BAC (mg %)	Cause of death	Autopsy findings
1	case	m/45	Negative	Cardiomyopathy	Severe cardiomyopathy- like lesions with 60 % narrowing of coronary lumen
2	case	m/57	Negative	Acute Myocardial Infraction	Cardiac hypertrophy, severe cardiomyopathy-like lesions, severe coronary atherosclerosis with 60-90% narrowing of coronary lumen
3	case	m/36	19	Cardiomyopathy	Severe cardiomyopathy- like lesions with 60 % narrowing of coronary lumen
4	case	m/34	Negative	Cardiomyopathy	Severe stenosis of cerebral artery, myocardial hypertrophy with dilated ventricles, cardiomyocadial-like lesions, moderated thickening of coronary artery
5	case	f/29	Negative	Acute Myocardial Infraction	Severe cardiomyopathy- like lesions, severe coronary atherosclerosis with 60-90% narrowing of coronary lumen
6	case	m/37	Negative	Cardiomyopathy	Severe cardiomyopathy- like lesions with 60 % narrowing of coronary lumen
7	case	m/35	Negative	Intracerebral hemorrhage	Intracerebral hemorrhage in cerebellum, Pulmonary edema and congestion of multiple organs, slightly thickening of coronary artery (20 %)
8	case	m/19	Negative	Intracerebral hemorrhage	Intracerebral hemorrhage in the right cerebral hemisphere
9	control	f/29	Negative	HIV infection	HIV infection, pulmonary edema, cerebral edema and congestion
10	control	m/30	Negative	Undetermined	No pathological findings
11	control	m/23	Negative	Undetermined	No pathological findings
12	case	m/41	Negative	Undetermined	Cardiac congestion and slightly thickening of coronary artery
13	case	m/55	Negative	Pulmonary infection	Pulmonary edema and infection
14	control	m/22	Negative	Undetermined	Multiple organs congestion
15	case	m/27	Negative	Undetermined	Cardiac hypertrophy, endocardial thickening in left ventricles 2.2 cm
16	case	m/40	Negative	Acute Myocardial Infraction	severe coronary atherosclerosis with 60-90% narrowing of coronary lumen
17	case	m/35	Negative	Acute Myocardial Infraction	Severe coronary atherosclerosis with cardiac hypertrophy

Undetermined = Undetermined cause of death with no pathological and toxicological findings,
BAC = Blood Alcohol Concentration

After completed autopsy, and all histopathological and toxicological examinations finished, the final report was interpreted again to summarize the cause of death. Adjusted causes of death and urine methamphetamine test were shown in Table 2. Subsequently, McNemar's chi-square was used to evaluate the risk relationship between using methamphetamine and cerebro-cardio vascular defects. The result of statistics test was shown in Table 3.

There were 15 discordant pairs (cases and controls had different exposure to the risk factors), 12 pairs (80%) where the controls was exposed to the risk factors but the cases was not, and 3 pairs (20%) where the cases was exposed to the risk factors but the control was not. The odds ratio was calculated as the ratio of these two values. In this study, the odds ratio for the association between risk factor and disease was 12/3 = 4, indicated that using methamphetamine was associated with a 4 folds increase in risk. The 95% confidence interval of odds ratio extended from 1.13 to 14.17 (Table 3).

Testing null hypothesis H_0: ÔR = 1 with McNemar's analysis, the two-tailed p value was equals to 0.035. By conventional criteria, indicated that there was a relationship between risk factor and disease with statistically significant.

Finally, some interesting autopsy data about positive methamphetamines were described in Table 4.

DISCUSSION: Methamphetamine abuse is also a social problem and public health hazards especially in Thailand. Most of the studies in other countries suggested that using methamphetamine might be one of risk factors for cerebro-cardiovascular defects. To clarify this relationship in Thai people, the authors performed matched pair case-control as a tool for study. Autopsy data were collected in cases of sudden unexpected death because most of the cases were related to cerebro-cardiovascular defects.

Magnitude of risk described in odds ratio (ÔR) in this study was equal to 4 that was consistent with findings of Westover *et al.* (OR=1.6) and Yeo *et al.* (OR=3.7) which studied in young adult patients and used of multiple logistic regression to analyze data[3,9]. It could be said that Thai people who are methamphetamine addicted tended to be cerebro-cardiovascular defects soon.

However, sensitivity or affinity of methamphetamine to induce cerobro-cardiovascular defects is not established. In Table 2, among prevalence of using methamphetamine in two "case" groups, cerebrovascular disease group (2.3%) was less than cardiovascular disease group (2.8%). The reason was perhaps that methamphetamine predominated severe adverse effect for cardiovascular more than cerebrovascular.

Autopsy finding of 6 cases that died from cardiovascular defects (Table4), showed that almost all cases had cardiomyopathy-like lesions, some cases showed cardiac infraction and some cases showed cardiac hypertrophy but all of them had same atherosclerotic condition. Although methamphetamine could induce cardiovascular complications in users with normal coronary arteries, various studies showed evidences that using methamphetamine could accelerate the development of coronary artery atherosclerosis, which increased the risk of myocardial infarction[10]. Moreover, chronic using has also been associated with ventricular hypertrophy, a condition that can predispose to methamphetamine -induced myocardial ischemia and/or arrhythmia[9]. A conclusion could be summarized that autopsy findings in this study corresponded with previous studies.

This study concluded that using methamphetamine could be a risk factor for cerebro-cardiovascular defects. This trend seemed to be a terrible problem and risk reduction procedure was important. It has been necessary for public authorities to realize and take action e.g. risk communication, to improve public understanding, promote self and community prevention to control those risks.

However, this study is limited to by cadavers that sent to autopsy at IFM only. That may be providing an underestimate data. Therefore, to perform a truly reflection about this risk in alive Thai populations, for the best, using a prospective cohort design which adequate sample sizes and selection of suitable cases from risk groups, for example some addicts from prison, hospital or

health station on addict treatment and rehabilitation.

REFERENCES:

1. United Nations Office on Drug and Crime. 2008. Amphetamine and Ecstasy 2008 Global ATS Assessment. Austria: United Nations Publication; pp. 27-32.

2. Office of the Narcotics Control Board. 2007. Situation of Substance Abuse. 2007. Bangkok: Jaransanitwong printing; pp. 23-4.

3. Yeo KK, Wijetunga M, Ito H, *et al.* 2007. The association of methamphetamine use and cardiomyopathy in young patients. Am J Med 120: 165–71.

4. Wako E, LeDoux D, Mitsumori L, Aldea GS. 2007. The emerging epidemic of methamphetamine-induced aortic dissections. J Card Surg 22: 390-3.

5. Yu Q, Larson DF, Watson RR. 2003. Heart disease, methamphetamine and AIDS. Life Sci 73: 129-40.

6. McGee SM, McGee DN, McGee MB. 2004. Spontaneous Intracerebral hemorrhage related to methamphetamine abuse autopsy findings and clinical correlation. Am J Forensic Med Pathol 25(4): 334-7.

7. Sharlene KS, McKetin R, Duflou J, Darke S. 2007. Methamphetamine and cardiovascular pathology: a review of the evidence. Addiction 102: 1204–11.

8. Moriya F, Hashimoto Y. 2002. A case of fatal hemorrhage in the cerebral ventricles following intravenous use of methamphetamine. Forensic Sci Int 129: 104-9.

9. Westover, AN, Nakonezny PA, Haley RW. 2008. Acute myocardial infarction in young adults who abuse amphetamines. Drug Alcohol Depend 96: 49-56.

10. Darke S, Kaye S, McKetin R, Duflou J. 2008. Major physical and psychological harms of methamphetamine use. Drug Alcohol Rev 27(3): 253-62.

11. Kongsakon R, Pocham N. 2007. Alcohol abuse and Domestic violence in Thailand: Matching case-control study. J Psychiatr Assoc Thailand 52(3): 291-300.