ORIGINAL ARTICLE

Cardiovascular effects of methamphetamine use disorder: A review of the epidemiology, etiopathogenesis, clinical presentation and management

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Methamphetamine (MA) abuse is a global problem with far reaching consequences on physical and mental health of those suffering from this menace. As far as the health complications of methamphetamine abuse are concerned, multiple organ systems undergo pathologic changes which manifest as wide array of clinical signs and symptoms. One of the most commonly affected organs is the heart. Cardiac complications are, in fact, the second leading cause of death in methamphetamine abusers. Cardiac conditions frequently seen in methamphetamine abusers include myocardial infarction, aortic dissection, arrhythmias, sudden cardiac death, malignant hypertension, cardiomyopathy with resultant congestive heart failure and pulmonary hypertension. Much to the relief of our medical community, however, methamphetamine abuse associated cardiomyopathy is potentially reversible. The key to reversibility of the cardiomyopathy is early detection followed by complete abstinence from methamphetamine use as well as the initiation of goal-directed therapy. The degree of cardiomyopathy reversal would depend on the total duration of methamphetamine use and the degree of myocardial damage at the time of diagnosis. The possibility of partial or even complete reversal of cardiac complication is an encouraging and reassuring medical fact which should be emphasized in patient counseling to motivate newly diagnosed patients of methamphetamine abuse to abstain from further abuse in the future. Our review aims to summarize the current literature on the cardiovascular complications of methamphetamine abuse, the various mechanisms of cardiac toxicity involved in the pathophysiology of methamphetamine abuse associated cardiomyopathy, the wide-ranging clinical presentations of the cardiomyopathy and the management options that are currently at our disposal.

Key Words: *Cardiovascular; Methamphetamine; Cardiomyopathy; Death*

INTRODUCTION

Methamphetamine (MA) is a psychostimulant amine which has both medicinal and recreational uses. Although methamphetamine is beneficial in treating psychiatric disorders, its use for recreational purposes (which typically involves higher and more frequent dosing) can cause detrimental effects on multiple organ systems, especially the central nervous, the cardiovascular and the gastrointestinal systems (1).

As a recreational drug of abuse, methamphetamine goes by several street names. The most commonly used names are "speed", "crack" "ice" and "crystal". It has two stereoisomers; the L-form or Levo-methamphetamine and the D-form or Dextro-methamphetamine. The later one is more potent and is the main constituent of the illicit form of the drug that is sold on the streets (2). Modes of administration used by methamphetamine abusers include intranasal, oral, rectal, inhalational and intravenous.

One of the most dangerous methamphetamine formulations sold on the street is crystal meth; it is a highly purified form of D-methamphetamine. It is available in powder form as well as in the form of clear crystal chunks. This form has been associated with higher incidence of dependence than the other forms of methamphetamine that are used recreationally (3,4).

Medical literature has already shed light on the molecular mechanism of action of methamphetamines It involves increased concentrations of norepinephrine, dopamine and serotonin in the central and peripheral nervous system synapses, which result from the following changes taking place at the synapses: increased neurotransmitter release, inhibition of neurotransmitter re uptake and inhibition of synaptic breakdown of neurotransmitters (5).

Pharmacokinetics

Methamphetamine is primarily metabolized in the liver. Its liver metabolites are amphetamine, 4-hydroxymetemphetamine, 4-Hydroxyamphetamine, norephedrine, 4-hydroxynorephedrine and hippuric acid. Methamphetamine is excreted through the kidneys. It is excreted predominantly in unchanged form (30-50%), followed by 15% as 4-hydroxyamphetamine, and 10% as amphetamine (1). Its detection in urine depends on the dose taken, the form used, and the urinary pH. Its repeated dosing tends to cause its accumulation in body tissues, resulting in its urinary excretion for a longer-than-usual (usual being up to three days after a single dose) period. Based on multiple studies, it is generally accepted that methamphetamine is detectable in urine for 1-3 days after the last dose of drug administration. Therefore, drug abstinence can be tested reliably by repeating urinalysis every 3-4 days (1,3).

Epidemiology

The global burden of methamphetamine abuse is concerning to say the least. The World Drug Reports 2018 revealed some alarming statistics, as highlighted in the remainder of this paragraph . An estimated 34.2 million people worldwide, or 0.7 cent of the population aged 15–64 years, admitted to having used methamphetamines in the past one year (6). Methamphetamine was also determined to be the second most commonly used drug worldwide, after marijuana. The highest prevalence of amphetamine use was reported in North America (2.0 per cent).

Although the lack of data from the other parts of the world makes it impossible to make a definitive assessment, it is believed that methamphetamine use is increasing and posing a significant threat to health in East and South-east Asian region. In the United States, methamphetamine use is most prevalent on the West Coast, and in the Midwest. Its use, however, is also spreading towards the Eastern part of the country (6).

The first national estimate of the economic burden of methamphetamine use in the United States was made using data from the year 2005. The analysis of data suggested an estimated national cost (of methamphetamine use) of $23.4 billion for that year. Moreover, the economic burden of the methamphetamine abuse is likely on the rise, since an increase in methamphetamine use-related visits to ED in the United States is suggestive of an increasing prevalence of methamphetamine abuse in the country (7).

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LITERATURE REVIEW

Etiopathogenesis of methamphetamine abuse-related cardiac damage

At the time of submission of this article, several studies are underway to elicit the mechanisms of chronic myocardial damage that results from methamphetamine use. However, no clear-cut mechanism has been established so far. One proposed explanation for MACM (methamphetamine associated cardiomyopathy) is chronic ischemia due to diminished myocardial perfusion reserve, in the setting of hypertrophied hearts. The ischemia results in myocardial damage due to diminished supply of oxygen and nutrients to the heart muscle. Since the hypertrophied myocardium in such cases is already vulnerable to ischemic damage, any amount of physical activity can trigger an ischemic episode by increasing myocardial oxygen demand. Aforementioned findings also provide a plausible explanation for the frequent angina episodes observed in patients who abuse methamphetamine (2,5,8,9).

One interesting study that we reviewed provided a comparison between cardiovascular pathophysiology of MACM and DCM (dilated cardiomyopathy). In this study, a group of MACM patients was compared with matched controls from DCM (dilated cardiomyopathy) group. The severity of myocardial inflammation in methamphetamine users was equally distributed among all users, regardless of the total duration of drug use. However, fibrosis was more pronounced in subjects with more prolonged drug use. On comparison with matched controls with DCM, the analysis revealed that inflammation was more pronounced in methamphetamine group, but fibrosis was more marked in DCM group, highlighting the role of inflammation in development of MACM. This study also highlighted the improvement in LV function that results from discontinuation of MA use (10).

Several studies have also pointed to oxidative stress as an important mechanism of cardiomyocyte damage in methamphetamine associated cardiomyopathy (11). In addition, a comparison with studies on pheochromocytoma patients provides another interesting proposition for the mechanism of MACM in the pathophysiology of MACM. Myocardium of pheochromocytoma patients shows similar histologic findings as the myocardium of MACM patients, with reversal of findings after treatment of the pheochromocytoma. Based on that information, some investigators have proposed that catecholamines are one of the culprits, most likely by an indirect mechanism rather than direct cardiotoxicity.

The most exciting information on the mechanism of cardiotoxicity in methamphetamine users comes from an experimental animal study. The findings of this study provide an exciting connection between the role of oxidative damage and the role of catecholamines in myocardial damage in patients who abuse methamphetamines. The study finds that myocardium damage is caused by high catecholamines levels. The study explains that high catecholamine levels cause oxidative stress by both direct and indirect mechanisms. Higher concentrations of catecholamines can result in catecholamine auto-oxidation by monoamine oxidase ultimately leading to production of superoxide free radicals (12,13). The indirect mechanism of catecholamine-mediated myocardial damage involves severe transient coronary spasm from catecholamine surge, with subsequent reperfusion injury through a series of changes that culminate in oxidative damage to myocytes.

Results from another study show direct cardiomyocyte contractile depression due to methamphetamine, possibly through protein damage and intracellular Ca^{2+} dysregulation.

An animal study, done using mice, has demonstrated that chronic methamphetamine administration promotes inflammation and atherosclerotic plaque formation in Apo E negative mice (14). More studies, including human studies, are needed to provide further evidence for this mechanism.

Vulnerability to methamphetamine associated cardiomyopathy (MACM) is also influenced by Cytochrome P450 polymorphisms, with extensive metabolizers appearing to be more prone to cardiotoxic effects of MA. It is unclear as to why patients develop different patterns of MACM, but it is probably an interplay of modifiers such as the route of administration, genetic polymorphisms, and co-ingestion of other substances (15).

Clinical presentation of methamphetamine abuse-related cardiovascular disease

Acute methamphetamine intoxication can present clinically important n several different ways, including the following: hypertensive urgency, malignant hypertension, aortic dissection, MI, methamphetamine associated cardiomyopathy (MACM), cardiogenic shock and endocarditis if IV drug use if involved (16). Repeated methamphetamine use over a period of time eventually leads to the development of pulmonary hypertension, cardiomyopathy, heart failure, and arrhythmias.

Acute aortic dissection

Acute aortic dissection, resulting from methamphetamine use, is thought to be due to a catecholamine surge causing hypertensive crisis and is well described in literature. This sudden adrenergic response is proposed to cause aortic wall shear stress leading to intimal tear (17). In a case series by Elizabeth et-al, the authors have suggested to routinely test for methamphetamine in patients less than 50 years of age (18). The management of acute aortic dissection involves, among other measures, good BP and HR control. There is also a need to abstain from the use of non-selective beta blockers in management of acute dissection or hypertension in methamphetamine users for reasons that are mentioned below in the "hypertension" section.

Hypertension

Methamphetamine can cause various degrees of hypertension ranging from hypertensive urgency to malignant hypertension. It has also been associated with chronic hypertension. The hypertension resulting from methamphetamine use is driven by an adrenergic response, which includes vasoconstriction from stimulation of alpha 1 receptors and tachycardia from stimulation of beta 1 receptors (4,16,17). Controlling BP in the setting of acute methamphetamine intoxication becomes even more important, in order to prevent the complications of the hypertensive response to the intoxication, such as aortic dissection and intracranial hemorrhage.

Since catecholamines act as agonists at alpha1, beta1 and beta2 receptors, it is recommended that non-selective beta blockers, such as propranolol, should be avoided in the pharmacological management of methamphetamine induced hypertension. This is because beta2 receptor blockade by a non-selective beta blocker can acutely worsen the hypertension by unopposed alpha1 receptor mediated vasoconstriction.

Based on literature, reasonable options to control BP in acute setting are vasodilators such as nitrates and nitroprusside, calcium channel blockers, selective alpha blockers such as phentolamine, and selective beta one receptor blockers (as adjunct). Based on literature on pheochromocytoma, calcium channel blockers have been shown to be effective in blunting the hypertensive response and tachycardia associated with catecholamine surge (8,19).

In one of the studies, authors have suggested sedation as the best initial management strategy, because it reduces intra synaptic level of catecholamine. The authors of the same study have proposed brain imaging to rule out intra cranial hemorrhage in patients in which hypertension is resistant to control (18). Other studies have proposed benzodiazepines as first line agents to control BP if hypertensive crisis is accompanied by CNS stimulation.

Some authors have suggested to avoid beta blockers to avoid unopposed alpha receptor related vasoconstriction. But there is no convincing evidence to avoid "selective" beta1 blockers in such a population (that is at risk of hypertensive crisis) including patients with methamphetamine intoxication/ abuse and patients with pheochromocytoma (20). Hence, we believe selective beta one blockers are a reasonable adjunct to above mentioned therapies to control hypertension in the acute setting especially when there is concern for aortic dissection. In the long term, a beta blocker with some alpha antagonist properties such as carvedilol is a reasonable choice.

Although there is a lack of data in the setting of methamphetamine related hypertension, literature on pheochromocytoma suggests two weeks of -antagonist therapy is adequate to facilitate safe introduction of -antagonists (8).

Acute coronary syndrome

Methamphetamine (MA) users often present with angina symptoms and palpitations. Although the exact mechanism is still unclear, it is believed to result from an interplay of multiple factors. Some of the proposed mechanisms include coronary artery spasm, plaque rupture, platelet aggregation, and thrombus formation (8,9,21). There are some case reports in literature which have demonstrated coronary artery spasm on angiograms (22). There are also case reports showing intracoronary thrombus formation, with one case report showing documented evidence of simultaneous thrombus of two coronary arteries. Other possible contributing factors could be a demand-supply gap driven by tachycardia or a reduction in myocardial perfusion

reserve in chronic methamphetamine users due to arteriole hypertrophy as well as perivascular and interstitial fibrosis (23). It is also pertinent to mention that existing risk factors for ACS will increase the risk of ACS in methamphetamine intoxication (24-26).

We believe a thorough approach should be taken in the assessment of methamphetamine users presenting with chest pain. Although chronic users can have a mild degree of troponin elevation from CMP and an acute stress response, cardiac CT or angiogram should be considered when suspicion for myocardial infarction is strong.

Arrhythmias and sudden death

MA is known to cause arrhythmogenic effects. Animal studies have shown a decrease in the expression of ion channels after *In-vitro* and *in-vivo* methamphetamine exposure and reversal of effects after discontinuation of methamphetamine (takes up to 8 weeks after the discontinuation of MA for reversal of effects to be complete). This reduction in ion channel expression has been proposed as a mechanism for electrical remodeling of the heart (27). Fibrosis associated with methamphetamine-induced cardiomyopathy can also trigger arrhythmias. Methamphetamine in lethal doses can also cause necrotic cell death in brainstem (Rostral Ventrolateral medulla), which leads to cardiovascular collapse by loss of cardiovascular regulation of brainstem (28). Hence cardiovascular collapse due to arrhythmias or cardiovascular collapse from brainstem death are two possible pathophysiological mechanisms for sudden death in methamphetamine overdose (26).

Pulmonary arterial hypertension

MA is a known cause of group one pulmonary hypertension. PAH in turn can cause right heart failure. A thorough history-taking is important in cases of suspected idiopathic PAH (17). One study in 2006 found that patients diagnosed with idiopathic PAH were 10.14 times more likely to have a history of methamphetamine use, compared to the general population (29). Counseling regarding cessation of methamphetamine use in such cases may help to reduce symptom burden and to improve treatment outcomes.

Methamphetamine associated cardiomyopathy (MACM)

Kalant, et al. first described the association between methamphetamine abuse and death from left ventricular (LV) failure in 2 people in 1975. Its incidence in the United States is increasing with more people using methamphetamine (MA), with most of the evidence coming from Australia and the United States.

Just like they were an important cause of idiopathic PAH in young patients, methamphetamines are a common cause of cardiomyopathy in young patients as well (in those with idiopathic cardiomyopathy). In one study by Yeo et al. they described 107 young patients with a new diagnosis of 'idiopathic' cardiomyopathy in whom subsequent interview and urinalysis revealed 40% prevalence of methamphetamine abuse (29).

MACM (methamphetamine associated cardiomyopathy) is roughly defined as a non-ischemic form of CMP in a MA using patient. MA use has been known to cause dilated cardiomyopathy (DCM), Takotsubo cardiomyopathy and reverse Takotsubo cardiomyopathy. MACM commonly presents with congestive heart failure with low EF (10,30). Multiple studies have shown that patients with MACM present in a more advanced stage of heart failure compared to patients with heart failure from some other cause of cardiomyopathy. There are also case reports of patients presenting with cardiogenic shock due to MACM, dying of MACM or requiring heart transplantation (22,31,32). However, it is difficult to rule out the confounding factors in the causation of MACM as several people with MA use also use alcohol and cocaine, which have been shown to worsen cardiac function in synergy with MA.

Patients with MACM are mostly young patients. Based on multiple studies most of the MACM patients present in their 30ies. On the other hand, alcoholic cardiomyopathy (49+11 years) and idiopathic Dilated Cardiomyopathy (52+13 years) commonly present in middle aged patients.

DISCUSSION

Management of methamphetamine abuse related cardiovascular complications

Monoclonal chimeric anti-methamphetamine antibodies have been tested in human subjects as a potential treatment for methamphetamine users. They have been shown to be safe in healthy subjects based on one of the studies. These high affinity and high specificity passive anti-meth-antibodies have been shown to effectively antagonize the CNS and CVS effects of MA by redistributing MA from CNS and directly neutralizing its effects. Further studies need to be done to provide evidence for effective clinical use of these antibodies (33,34).

Management of methamphetamine associated cardiomyopathy

MACM should be treated per current guidelines for other types of cardiomyopathies. An echocardiogram should be obtained based on clinical judgement when there is change in clinical status of the patient. Having said that, ICD implantation should be considered carefully taking into account other factors involved such as: IV drug use with risk of device infection, compliance to goal directed medical therapy, and other co morbidities.

A subset of MACM patients with less ventricular dilation and RT (Reverse Takotsubo) pattern tend to recover their ventricular function early after MA cessation. In contrast, those with more marked fibrosis and a greater degree of cardiac chamber dilation have limited scope of recovery (35).

There is strong evidence documenting improvement in cardiac function and resolution of symptoms after cessation of MA use. One study showed improvement in NYHA class in 55.6% of patients who discontinued the drug compare to 7.7% who continued MA use. The average time for improvement in class function was 8 weeks (range 1-12 weeks) in patients with reliable follow up and clear discontinuation date (36).

CONCLUSION

Methamphetamine abuse can have adverse and far reaching consequences for the cardiovascular health of the methamphetamine users. These methamphetamines associated cardiovascular diseases can lead to significant morbidity and mortality, with extra burden on the resources of our healthcare system. As a result, there is a dire need for public awareness campaigns to spread information on the adverse health consequences of methamphetamine abuse. The is also a need for the government to facilitate the law enforcement agencies in maintaining a strict control over the illegal distribution and sale of methamphetamine. Therefore, in a nutshell, all the different stakeholders (physicians, social workers, law enforcement agencies and the government) need to work together to rid the society of the harmful health effects of methamphetamine abuse

DECLARATIONS OF INTEREST

None.

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