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Comparative hazards of acute myocardial infarction among hospitalized patients with methamphetamine- or cocaine-use disorders: A retrospective cohort study

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ABSTRACT

Background: It is assumed that recreational use of methamphetamine can trigger acute myocardial infarction (AMI) events, but estimates of longitudinal hazards of AMI among methamphetamine users are lacking.
Methods: Retrospective cohort study: Competing-risks analysis was used to estimate time-to-AMI patterns in methamphetamine versus matched appendicitis (population-proxy) and matched cocaine (drug-control) groups. Cohorts were propensity-score-matched using demographic and clinical variables.
Setting: California, 1990–2005.
Participants: Cohorts of individuals with no prior or concurrent history of AMI hospitalized with methamphetamine- (n = 73,056), cocaine- (n = 47,726), or appendicitis-related conditions (n = 330,109).
Measurements: ICD-9/ICD-10 indications of AMI (ICD-9 410.X; ICD-10 I21.X) in death records or inpatient hospital data.
Results: Patients in methamphetamine cohort were more likely to develop subsequent AMI in comparison to those in matched appendicitis cohort [Hazard ratio (HR): 1.41; 95% CI, 1.23–1.62, $p < 0.0001$], with increased risk most marked in young methamphetamine users (age 15–34 years; HR: 2.04; 95% CI, 1.63–2.57, $p = 0.0001$). Risk was slightly increased vs. that in matched cocaine group (HR: 1.19; 95% CI, 1.02–1.39, $p = 0.029$). Individuals in cocaine cohort were also more likely to experience AMI outcome vs. appendicitis cohort (HR: 1.25; 95% CI, 1.08–1.45, $p = 0.0023$).
Conclusion: Our longitudinal data support results of earlier epidemiological studies suggesting that persons with methamphetamine- (or cocaine-) use disorders might have increased AMI risk. However, because of potential study limitations and the unexpectedly modest magnitude of the observed increased AMI hazard, these findings must be considered preliminary and require replication.

1. Introduction

Amphetamine-type stimulants – a drug class comprised primarily of methamphetamine and amphetamine – are widely used stimulants taken for both recreational and, at lower doses, therapeutic purposes (e.g., treatment of attention deficit hyperactivity disorder) (Kish, 2008). Recently, in a large-scale cohort study, we showed that individuals with methamphetamine-use disorders had higher all-cause mortality risk than did users of the related psychostimulant cocaine, as well as those of alcohol, and cannabis, but lower than that of opioid users (Callaghan et al., 2012). Similarly, using a broad "harm" scale, methamphetamine use was found by a group of European Union drug experts to score high on "harm to users" (van Amsterdam et al., 2015). However, the actual quantitative extent of increased risk of toxicity of methamphetamine to different organ systems in the human (e.g., the heart) is still debated and uncertain.

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It is assumed that methamphetamine would likely cause severe adverse effects on the cardiovascular system in some users, in part through increased catecholamine release, blood pressure, heart rate, oxygen demand, and vasoconstriction of coronary arteries (Karch et al., 1999; Karch, 1999; Karch, 2007; Darke et al., 2008). For example, in extensive post-mortem investigations, coronary disease conditions were identified as common features of methamphetamine-related deaths (Karch, 1999; Darke et al., 2017). Thus, it would be reasonable to expect that recreational methamphetamine use should also increase risk of acute myocardial infarction [AMI; myocardial cell death due to ischemia (Thygesen and Searle, 2013)], an acute life-threatening condition significantly associated with mortality, morbidity, hospitalization, and hospital re-admission (Ruff and Braunwald, 2011; Krumholz et al., 2013; Castro-Dominguez et al., 2018; Tran et al., 2017). Surprisingly, however, Karch (1999) noted that "reports of methamphetamine-related myocardial infarcts remain so uncommon as to still be reportable" and, more recently, opined that such methamphetamine-related infarcts are "much less common" than those related to the stimulant cocaine "even though clinical and autopsy experience generally suggest that methamphetamine abusers are just as likely to develop an accelerated form of [coronary artery] disease as cocaine abusers" (Karch and Drummer, 2015).

The available literature on methamphetamine and AMI risk largely consists of AMI proportion estimates amongst users in, for example, hospital-based case series, case studies, or postmortem reports (Costa et al., 2001; Turnipseed et al., 2003; Wijetunga et al., 2004; Kaye et al., 2007; Yeo et al., 2007; Cruickshank and Dyer, 2009; Darke et al., 2017). Interpretation of these findings, although suggestive, are uncertain because of the lack of a quantitative assessment of incidence, for which longitudinal studies are essential. Surprisingly, few systematic studies have been conducted to estimate the actual hazard of incident AMI amongst methamphetamine users. To our knowledge, the only population-based epidemiological investigation of recreational methamphetamine use and AMI is a cross-sectional investigation (Westover et al., 2008) that did not permit calculation of comparative longitudinal hazards of AMI among persons with methamphetamine-use disorders in relation to those of other stimulant controls or population-proxy controls. In a recent 10-year retrospective cohort study of methamphetamine users admitted to inpatient psychiatric hospital in Taiwan, Huang and colleagues (2016) found no evidence of increased hazard of incident acute coronary syndromes (ACS; an ICD-9-based category including myocardial infarction) in the methamphetamine-use cohort; however, this Cox-model estimate was severely compromised by insufficient ACS outcomes ($n = 1$) in the analyses.

Our longitudinal population-based study of methamphetamine users, incorporating a competing risks design (which accounts for the potential differences in mortality patterns across cohorts) and a proxy control group, aims to address literature deficiencies. The study also includes, for comparison and possible insight into mechanism, a group of users of the related stimulant cocaine. Based on suggestive literature findings, we hypothesized that individuals hospitalized with methamphetamine-use disorders would have significantly greater likelihood of subsequent readmission or death attributed to AMI in relation to: (1) a population-proxy control group comprised of individuals receiving an inpatient appendicitis-related diagnosis; and (2) individuals hospitalized with a cocaine-use disorder. Based on the differing pharmacokinetic properties of (longer-acting) methamphetamine vs. cocaine, we tentatively hypothesized that the risk of AMI in methamphetamine users might be higher than that of cocaine users.

2. Methods

2.1. Data sources: California's Hospital morbidity dataset, 1990–2005; California Vital Statistics Database, 1990–2005.

The current study, which was approved by the Centre for Addiction and Mental Health Research Ethics Board, used anonymized Office of Statewide Health Planning and Development (OSHPD) California inpatient hospital admission data from January 1, 1990 until December 31, 2005 from the Patient Discharge Database (PDD). The dataset consisted of a record containing demographic information and up to 25 diagnoses, based on the International Classification of Diseases, 9th edition (ICD-9), for each inpatient discharge from a California licensed hospital; that is, general acute care, acute psychiatric, chemical dependency recovery, and psychiatric health facilities, but excluding federal hospitals. Inpatient data were screened by an automated data entry and reporting software (MIRCal), and data fields with error rates of 0.1% or higher were returned to the hospitals for correction (Zach, 1990; California Office of Statewide Health Planning and Development, 1995). Reabstraction studies comparing OSHPD inpatient data files with original medical records have found specificities for diagnoses ranging from 0.98 to 1.00, and sensitivities for diagnoses ranging from 0.88 to1.00 (California Office of Statewide Health Planning and Development, 1990; California Office of Statewide Health Planning and Development, 1996; Romano et al., 1996).

Death records from the California Vital Statistics Database (VSD; which captures all death records for the state) were linked to the Patient Discharge Database inpatient data. The probabilistic matching algorithm linking California inpatient records to state death records has a linkage sensitivity and specificity of 0.9524 and 0.9998, respectively, and positive and negative predictive values of 0.994 and 0.998 (Zingmond et al., 2004).

2.2. Measurement of outcome: acute myocardial infarction

The primary outcome variable was time from index admission until (1) diagnosis of acute myocardial infarction (ICD-9 410.X; ICD-10 I21.X) in subsequent inpatient records (in any diagnostic position) or listing of acute myocardial infarction as underlying cause of death in the VSD; or (2) time of death; or (3) the study end date, if the patient was censored.

2.3. Cohort assignment algorithms

2.3.1. Methamphetamine group assignment

Patients were assigned to the methamphetamine group only if they had the following characteristics: (1) an ICD-9 diagnosis, in any diagnostic position, of 304.4 (amphetamine dependence), 305.7 (amphetamine abuse), 969.7 (amphetamine poisoning) and E854.2 [accidental (unintentional) amphetamine poisoning]; (2) no prior or concurrent indication (in relation to their index admission) of AMI; and (3) no prior, concurrent, or subsequent ICD-9 indication of any alcohol or drug use other than methamphetamine (using the exclusionary ICD-9 codes in Table 1).

2.3.2. Cocaine group assignment

Patients were assigned to the cocaine group only if they had the following characteristics: (1) an ICD-9 diagnosis, in any diagnostic position, of 304.2 (cocaine dependence), 305.6 (cocaine abuse), 968.5 (cocaine poisoning), or E855.2 (accidental cocaine poisoning), with the earliest ICD-9 cocaine diagnosis indicating the index admission; (2) no prior or concurrent indication (in relation to their index admission) of AMI; and (3) no prior, concurrent, or subsequent ICD-9 indication of any alcohol or drug use other than cocaine (using the exclusionary ICD-9 codes outlined in Supplementary Table S1).

2.3.3. Appendicitis group assignment

Individuals with an appendicitis-related inpatient diagnosis (in any diagnostic position) served as the population-proxy comparison group because (1) appendicitis is a relatively frequent reason for admission to hospital; (2) it is not associated with socioeconomic status (Poikolainen et al., 1985; Primatesta and Goldacre, 1994; Hale et al., 1997); (3)