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Short communication

Burden of arrhythmia in hospitalizations with opioid overdose☆

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ABSTRACT

Background: Opioid overdose-related hospitalizations continue to rise in the United States. These hospitalizations are frequently associated with arrhythmia which can increase in-hospital mortality and resource utilization. We describe temporal trends in the hospitalizations for opioid overdose, associated arrhythmias, and their impact on in-hospital mortality, length of stay and cost of hospitalizations. The purpose of this study was to identify incidence of arrhythmia and their impact on in-hospital outcomes with opioid overdose hospitalizations.
Methods: The study utilized data from the National Inpatient Sample from January 2005 to September 2015. Previously employed International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes were utilized to identify opioid overdose and associated arrhythmias. The analysis was performed using SAS (SAS Institute Inc., Cary, NC). Temporal trends were measured using Jonckheere-Terpstra Trend test.
Results: A total of 430,460 adult hospitalizations with opioid overdose were included in this study. Atrial fibrillation ($N = 17{,}695$, 4.1%) was the most frequent arrhythmia associated with opioid overdose, the trend of which increased significantly during the study period. All-cause in-hospital mortality increased substantially with arrhythmias, highest with ventricular fibrillation and ventricular tachycardia. The incidence of arrhythmias was associated with longer length of stay and higher cost of hospitalizations as well.
Conclusions: Incidence of new-onset arrhythmia with opioid overdose lead to higher in-hospital mortality which can further increase the length of hospitalization and cost of care.

Opioid overdose-related admissions increased to 4-fold in the last decade, and it continues to rise [1]. Opioid overdose-related hospitalizations are frequently associated with arrhythmias which require extensive work up in the hospital [2]. There is not enough data demonstrating the temporal trends of arrhythmias associated with opioid overdose. In this study, we describe temporal trends in the hospitalizations for opioid overdose, associated arrhythmias, and their impact on in-hospital mortality, length of stay and cost of hospitalizations.

This study includes hospitalizations from the National Inpatient Sample (NIS) which is a 20% stratified sample of all hospital admission from the United States. This database has been explained in the past [3,4]. We included hospitalizations from January 2005 to September 2015 to be able to identify hospitalizations using *International Classifications of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes. This study included previously utilized ICD-9-CM codes to identify study population [5]. To identify hospitalizations with opioid overdose, we only included ICD-9-CM codes in the primary diagnosis column. This strategy may have led to underreporting of opioid overdose hospitalizations. We excluded all hospitalizations below 18 years of age. New-onset arrhythmias were identified using ICD-9-CM diagnosis codes in the secondary columns. We utilized 427.31 for atrial fibrillation, 427.32 for atrial flutter, 427.0 for supraventricular tachycardia, 427.41 for ventricular fibrillation, 427.42 for ventricular flutter, 427.1 for ventricular tachycardia which has been utilized previously [6]. All analyses were performed using SAS 9.4 which accounted for the complex survey, stratification, and clustering per recommendation. Cost and length of stay were demonstrated using median with interquartile range as the data distribution was non-normal. Categorical data was demonstrated in frequency. This study utilized Jonckheere-Terpstra trend analysis for measurement of the trend from January 2005 to September 2015. All the frequency was expressed per 1000 opioid overdose hospitalizations. This study was considered exempt from the institutional review board review as it consisted of de-identified hospitalizations.

A total of 430,460 adult hospitalizations with opioid overdose were included in this study. Atrial fibrillation ($N = 17{,}695$, 4.1%) was the most frequent arrhythmia followed by ventricular tachycardia ($N = 3102$, 0.72%), atrial flutter ($N = 1548$, 0.36%), ventricular fibrillation/flutter ($N = 1155$, 0.27%) and supraventricular ventricular tachycardia

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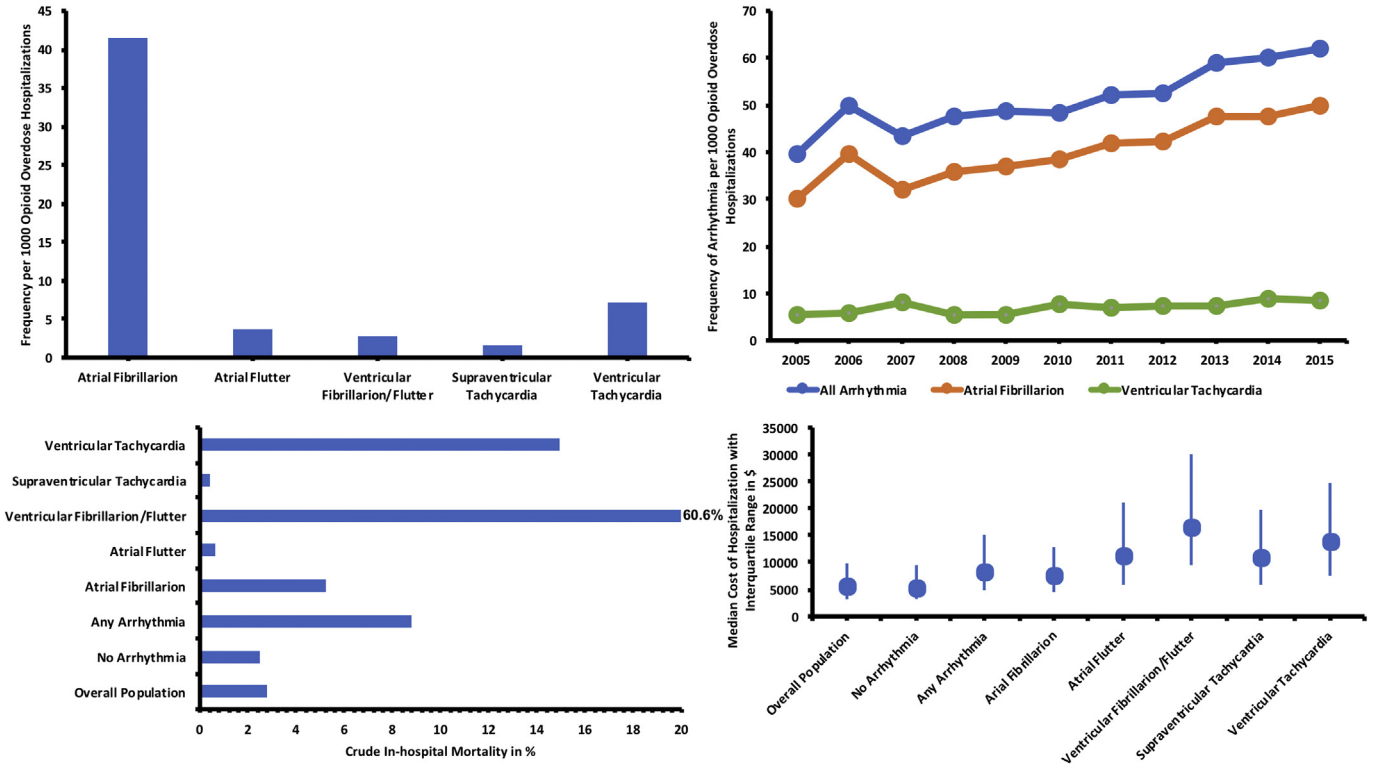

Fig. 1. Frequency of arrhythmia, their trend from 2005 ro2015, associated in-hospital mortality and cost of hospitalization. Panel A: Frequency of arrhythmia per 1000 hospitalizations for opioid overdose. Panel B: Trends of any arrhythmia, atrial fibrillation and ventricular tachycardia per 1000 opioid overdose hospitalizations from January 2005 to September 2015. This excludes trends of atrial flutter, ventricular fibrillation/flutter and supraventricular tachycardia as frequency was very low for trend measurement. P_{trend} value for any arrhythmia, atrial fibrillation and ventricular tachycardia was <0.001. Panel C: All-cause in-hospital mortality associated with arrhythmia. Panel D: Median cost with interquartile range for hospitalizations associated with arrhythmia.

($N = 658$, 0.15%) (Fig. 1, Panel A). Trend in the hospitalizations with any arrhythmia (39.5 to 62 per 1000 hospitalizations, $P_{trend} < 0.001$), atrial fibrillation (30 to 50 per 1000 hospitalizations, $P_{trend} < 0.001$), and ventricular tachycardia (5.5 to 8.5 per 1000 hospitalizations, $P_{trend} < 0.001$), significantly increased during the study period (Fig. 1, Panel B). In-hospital mortality in overall opioid overdose hospitalizations was 2.8% and 2.5% in those without any arrhythmia. This increased to 8.8% in those with any arrhythmia. All-cause in-hospital mortality was highest with ventricular fibrillation/flutter (60.6%) and ventricular tachycardia (14.9%) as expected. In-hospital mortality almost doubled in those with atrial fibrillation (5.2%) (Fig. 1, Panel C). The median length of stay was two days in overall population which increased to 3 days with any arrhythmia and atrial fibrillation, and highest with atrial flutter and ventricular tachycardia (5 days). The median cost of hospitalizations was $5408 with overall hospitalizations, $8208 with any arrhythmia, $7436 with atrial fibrillation, $11,043 with atrial flutter, $16,519 with ventricular fibrillation, $13,928 with ventricular tachycardia (Fig. 1, Panel D).

This analysis demonstrates a significant increase in the opioid overdose hospitalizations and associated arrhythmias, especially atrial fibrillation and ventricular tachycardia. In a previous study by Qureshi et al. demonstrated increased prevalence of atrial fibrillation with opioid use [2]. The reason for increased arrhythmias with opioid overdose is largely unknown. However, the proposed mechanism was that endogenous opioid-peptide open K + ATP channels making it resistant to oxidative stress during the episodes of ischemia which might let atrial-myocytes damage the heart muscles and cause atrial fibrillation [2,7]. We found that the prevalence of atrial fibrillation is much higher than general population [8]. Another study done in Taiwan demonstrated higher risk of developing atrial fibrillation in female patients taking morphine [9]. The in-hospital mortality rates were increased to almost four-fold with any arrhythmia as compared to no arrhythmia group. It also increased significantly in those with atrial fibrillation, ventricular fibrillation/flutter and ventricular tachycardia group. The incidence of this arrhythmias required extensive workup which further extends their hospitalizations stay and in turn increase the cost of care. The total economic burden associated with opioid overdose, abuse and dependence were thought to be $78.5 billion per annum in 2013 out of which one-third was directly associated with health care and treatment cost [10]. The physician should assess the risk for misuse, suicide, or abuse before prescribing opioid for pain management. We recommend early identification using telemetry for admitted patients, increase access to the treatment and reversal agents in addition to prompt treatment of such arrhythmias.

Several limitations associated with this study as we did not account for emergency visits, outpatient visits, opioid overdose during hospitalizations and coding errors. Other limitations of the NIS include but not limited to cause of death, follow-up, readmissions, and medications. The arrhythmogenicity of different opioid differ and we do not have information on the type of opioid medication used and indication for the use of opioid [11]. According to previous literature search, methadone carries a highest risk, tramadol and oxycodone belongs to intermediate risk and morphine and buprenorphine belongs to lower risk for arrhythmia [11]. Additionally, we do not have information on the QT interval prolongation due to limitations associated with NIS database. However, this is largest till date, a nationally representative study demonstrating the burden of arrhythmias in hospitalizations with opioid overdose.

In summary, trends of arrhythmias associated with opioid overdose was increasing. Most common arrhythmia associated with opioid overdose was atrial fibrillation. Incidence of new arrhythmias was also associated with higher in-hospital mortality, longer length of stay and significantly higher economic burden.

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Conflict of interest

None. The authors have no conflict of interest.

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