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Opiate Injection-associated Infective Endocarditis in the Southeastern United States

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Abstract

Background—Opiate pain reliever (OPR) misuse by injection is increasing in the United States. Infective endocarditis (IE), a devastating complication of injection OPR use, has been understudied.

Methods—We conducted a retrospective chart review of IE cases at an academic tertiary care hospital in North Carolina. Hospital admissions from 2009–2014 were screened for cases of definite IE. Subjects reporting injection drug use (IDU) were classified as IDU-IE, and compared to those without reported IDU, classified as No IDU-IE. Rates of IDU-IE and No IDU-IE, patient demographics, microbiologic data and outcomes were compared between the groups.

Results—A total of 127 incident admissions for IE were identified, 48 (37.8%) were classified as IDU-IE and 79 (62.2%) as No IDU-IE. IDU-IE cases increased from 14% of hospitalizations for IE in 2009 to 56% in 2014; reporting of OPR injection increased in 2012 and continued through the study period. IDU-IE subjects were younger (32.6 ± 11.7 versus 54.4 ± 13.1 , $P < 0.0001$), more likely to be single ($n = 33$ [68.8%] versus $n = 23$ [29.1%], $P < 0.0001$) and to reside in rural communities ($n = 36$ [75.0%] versus $n = 25$ [31.6%], $P < 0.0001$) than No IDU-IE subjects. Hospital length of stay (26 days versus 12 days, $P < 0.0001$) and intensive care unit length of stay (2 days versus 1 day, $P = 0.04$) were longer for IDU-IE patients and hospital mortality did not differ (10.4% IDU-IE versus 8.9% No IDU-IE, $P = 0.77$).

Conclusions—IDU-IE rates increased over time, and OPR injection use in rural communities appears to be a major contributor. Interventions to reduce IDU-IE and OPR misuse are needed to halt this growing epidemic in at-risk rural communities.

Key Indexing Terms

Injection drug use; Oxycodone; Critical care; Infection; Opana

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INTRODUCTION

Opiate pain reliever (OPR) prescribing has increased substantially over the past 15 years in the United States, and OPR overdoses and deaths in this country have outpaced those from heroin and cocaine.^{1–3} OPR overdoses and injection drug use (IDU; via subcutaneous or intravenous injection of crushed pills or other substances) began to rise in the early 2000s, particularly in rural communities.^{4,5} More recently, OPR IDU has received significant attention because of its association with a community outbreak of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections in rural communities in the Mid-west and Southeast U.S.^{6,7} At our tertiary care academic medical center in north central North Carolina, we anecdotally observed an increase in the frequency of hospitalizations related to OPR IDU.

One of the most devastating consequences of IDU is the development of infective endocarditis (IE). IE is an infection of the endocardial surface of the heart in which an infected thrombus, or vegetation, forms on the native or prosthetic valve in the setting of bacteremia and endothelial damage. IE is associated with organ failure, prolonged hospitalization, high cost and death in up to a quarter of patients.^{8,9} Unsterile practices during preparation and injection of OPRs that introduce skin and oral bacteria into the bloodstream may be one mechanism for the increased risk of IE in this population.^{10,11} Although HIV and HCV outbreaks among OPR injection drug users have received significant media attention, studies examining IE in these patients are lacking. Therefore, to identify temporal trends, demographics and outcomes of IE at our hospital and to examine the temporal association of IE with IDU, we performed a retrospective chart review of hospitalizations related to IE at our medical center from 2009–2014.

METHODS

Study Location

The study was conducted at Wake Forest Baptist Medical Center (WFBMC), an 850-bed academic medical center with approximately 42,000 hospital admissions per year located in Winston-Salem, NC, U.S.A. It serves as a tertiary care medical center for the surrounding north-central region of North Carolina and rural areas of western Virginia, West Virginia, and eastern Tennessee.

Study Design

This study was approved by the Wake Forest School of Medicine Institutional Review Board. Subjects were identified initially by screening the hospital database for admissions to WFBMC for patients aged 18 years or older hospitalized with primary ICD-9 codes for IE from January 1, 2009 to August 31, 2014. ICD-9 codes used to screen hospital records were 421.0, 421.1, 421.9, 424.90, 424.91 and 424.99. Cases of IE identified by ICD-9 were verified by individual chart review. Patients were only classified as having IE if they met the modified Duke Criteria for definite IE.¹² For patients with recurrent admissions to WFBMC for IE, only the initial hospitalization during the study period was recorded. IDU-IE was defined if IDU was acknowledged by the patient and documented in the medical record

during that hospitalization. For those cases in which there was high clinical suspicion for IDU though denied by the patient, the hospitalization was classified as IDU-IE if the patient had a history of IDU and associated bacteremia documented in the year before index hospitalization at our medical center. The definition of IDU-IE was determined *a priori* individual chart review. Cases without IDU criteria were classified as No IDU-IE. The incidence of total IE cases during the study period was normalized to hospital admissions over each interval to determine if new IE cases represented a change in IE incidence or the overall rate of hospital admissions.

Study Variables

Patient demographics and clinical data were obtained from the medical chart for each case of IE meeting the above criteria during the study period. Counties of residence were classified as rural or nonrural based on delineations from the United States Office of Management and Budget from 2013 (<http://www.census.gov/population/metro/>).

Statistical Analysis

Data are reported as mean $\pm$ standard deviation or n (%) or Kaplan Meier estimated median and interquartile range as indicated. Comparisons of groups were made using a two-sample t test or a chi-square test for continuous and categorical variables respectively. In determining discharge location, those who died in the hospital were censored. Hospital LOS and intensive care unit (ICU) LOS were compared by the log-rank test. Hospital mortality was a dichotomous variable compared using a chi-square test.

RESULTS

A total of 127 incident admissions to our hospital for IE were identified between January 2009 and August 2014. Of them, 48 (37.8%) were classified as IDU-IE. The remaining 79 (62.2%) were classified as No IDU-IE. Incident IDU-IE cases increased over the study period, with IDU-IE accounting for 14% of hospitalizations in 2009 and increasing to 56% in the last 4 quarters of our study period (Figure A). We also found an upward trend in both IDU-IE and No IDU-IE cases over the 2013 calendar year, with a doubling of total IE rates compared to other time periods (Figure A). During the study period from 2009 through the third quarter of 2012, we identified only one reported case of OPR injection (oxycodone) in the IDU-IE group. During the fourth quarter of 2012 through 2014, we identified an increase in reporting of OPR injection use, primarily oxymorphone (Opana) and oxycodone (Figure B). The increase in cases of IE beginning in late 2012 coincided simultaneously with the increased reporting of OPR injection use.

Baseline characteristics of the study cohort are reported in Table 1. IDU-IE patients were younger than those without identifiable IDU (32.6 ± 11.7 versus 54.4 ± 13.1 years, $P < 0.0001$). No differences were found in sex and race or ethnicity between the groups, though IE patients were more likely to be male (68.5%) and white (88.2%). Marital status also differed between the groups ($P < 0.0001$)—IDU-IE patients were more likely to be single than No IDU-IE patients (68.8% versus 29.1%). County of residence differed between the

groups with more patients in the IDU-IE cohort residing in a rural county (75.0% versus 31.6%, $P < 0.0001$).

The identified bacterial isolates differed between the 2 groups (Table 2, $P = 0.0009$). *Staphylococcus aureus* (both methicillin-sensitive and resistant strains) was most common in IDU-IE patients ($n = 25$ [52.1%] versus $n = 16$ [20.2%]), whereas *Streptococcal* species were more common in the No IDU-IE patients ($n = 41$ [52.0%] versus $n = 12$ [25.1%]). Coagulase-negative staphylococcus, gram-negative rods, polymicrobial infections and other organisms accounted for the remaining isolates.

Table 3 lists the outcomes of both groups. IDU-IE patients had longer median hospital length of stay (LOS) (26 versus 12 days, $P < 0.0001$) and a longer ICU LOS (2 versus 1 days, $P = 0.04$). Ventilator-free survival did not differ between groups and was 77% and 80% respectively for IDU-IE versus No IDU-IE subjects ($P = 0.72$). Discharge location, the need for renal replacement therapy or surgery for IE did not differ between the groups. In-hospital mortality was also similar between the 2 groups. The overall in-hospital mortality was 9.4% and did not differ between the groups.

DISCUSSION

In this study, we found an increase in both the incidence of IDU-IE per hospital admission and the percentage of IDU-IE to total IE over time during the study period. IDU-IE cases increased over time in our study, further substantiating national reports of increased IDU-associated comorbidities.¹³ From 2009 to mid-2012, there were very few cases of IDU-IE seen in our medical center. We found that the increase in total IE and IDU-IE cases in 2012–2014 temporally correlated with patient reports of OPR IDU, whereas the rates of reported heroin use in IE patients remained stable and relatively low throughout the study period. IDU-IE patients were more likely to come from rural communities, similar to other recent reports documenting an increase in OPR IDU in rural communities in the U.S., including its association with outbreaks of HCV and HIV in rural communities across the South and Midwest.^{4,6,7,14,15} One reason for the high rates of OPR IDU may relate to regional availability of these drugs. In our region, OPR prescribing rates are high.¹ North Carolina ranked 13th overall in OPR prescriptions in the U.S. in 2012. Rates of OPR prescription in the surrounding region are also high; Tennessee ranks 2nd, West Virginia ranks 3rd and Virginia ranks 29th.¹⁶ Reasons for the high variability of prescribing rates of OPRs in the U.S. are poorly understood. However, the increased prescribing rates and availability of OPRs in our region may be one factor contributing to the surge in IE cases observed in this study.

Injection drug users in this study primarily reported injecting oxymorphone and oxycodone. Oxymorphone misuse is particularly problematic in our area, and it was the most frequently reported drug in the IDU-IE patients in our study (37% of cases reporting a specific drug mentioned oxymorphone). The oral formulation of oxymorphone, Opana (both extended release and immediate release), came to market in 2006 and was subsequently modified to be abuse deterrent in 2012 by incorporating a polyethylene oxide matrix designed to resist crushing.¹⁷ Oxymorphone has received recent attention because of infectious and noninfectious complications related to injection use. In 2012, at our center and others,

reports appeared of a microangiopathic hemolytic anemia seen in some patients with oxymorphone injection, specifically the abuse deterrent extended release formulation.^{18–22} Additionally, most patients involved in the recent outbreak of HIV in rural Indiana reported oxymorphone IDU.⁶ Reportedly, misuse of oxymorphone was also a potential problem in its previous oral formulation, NuMorphan, in the 1960s and 1970s before it was withdrawn from the market.²³

It is unclear if the high rates of oxymorphone IDU-related IE in our study stem exclusively from increased availability of oxymorphone in the region, or if there are specific characteristics of the formulation that increase the risk of developing IE. For instance, some injected foreign materials are postulated to increase the risk of developing endocarditis due to particulate-host interactions leading to endothelial damage or immune complex formation.¹⁰ Additionally, unsterile practices during preparation and injection, including crushing or dissolving tablets, licking needles and sharing drug preparation equipment, increase the risk of IDU-associated bacteremia.^{11,24} This may be particularly relevant for tamper-resistant formulations of OPRs, which aim to reduce oral opioid misuse via alternate routes of ingestion,²⁵ but might inadvertently lead to additional user manipulation of the pills to circumvent these abuse-deterrent mechanisms. It is possible that increased “handling” of pills by users may increase the risk of bacterial contamination of the pill fragments. Further study would be needed to determine if specific characteristics of the oxymorphone formulation or the way in which it is prepared for injection predispose users to higher rates of developing IE. Another interesting observation of our study is the relatively low rate of reported heroin use in the IDU-IE patients, despite an increase in heroin use and overdose deaths in North Carolina during the same time period reported by others.²⁶ We are unclear about the significance of this finding, but perhaps the increased “handling” or pharmacologic characteristics of the pills lead to a higher risk of IE in those injecting oral opiates as compared to those injecting heroin. Alternatively, the stigma associated with heroin use may have led to patient underreporting of its use in this study.

The outcomes of the IDU-IE in our cohort highlight the significant morbidity and mortality associated with IDU-IE. Despite IDU-IE patients being significantly younger than No IDU-IE patients (33 versus 54 years), IDU-IE patients had increased ICU and hospital LOS. In this young group of patients, ~10% died, and 35% underwent cardiac surgery. Discharge location did not differ ($P = 0.30$), though there was a numerically lower percentage of IDU-IE patients discharged home (51.2% versus 66.7%) and a higher percentage discharged to a skilled nursing facility or long-term acute care facility (37.2% versus 23.6%). In a large international study of IE conducted from 2000–2005, the median age of IE was 58 years, similar to the age of our No IDU-IE cohort.²⁷ We found no significant differences in race between the two groups, though the IDU-IE group was nearly exclusively white (98.4% versus 83.5%).

Collectively, these striking differences in demographics and outcomes highlight the changing epidemiology of IDU in the Southeast U.S., which has shifted to younger patients from rural communities. These temporally changing demographics are consistent with recent reports of increased all-cause mortality in middle-aged whites over the past decade, which is associated with increased drug use, alcohol poisoning and suicide.²⁸ Our study adds to the

recent reports of increasing IDU-related comorbidities in rural communities, suggesting particular vulnerability of this population that may be related to socioeconomic and cultural factors, reduced access to harm-reduction measures such as syringe-exchange programs, or lack of availability of mental health and substance abuse services in these rural areas.

There are limitations to our study. The retrospective nature of the design may have misclassified patients into either group, as not all patients may have been directly asked regarding IDU during their hospitalization. We attempted to limit misclassification by applying strict *a priori* criteria to define cases of IDU. These strict definitions may have underestimated, not overestimated the proportion of IDU-IE cases seen during the study interval owing to patient underreporting or lack of provider documentation. An additional limitation includes the possibility that the increase in-hospital LOS in IDU-IE subjects could be accounted for by reluctance of providers to allow patients reporting IDU to go home with intravenous catheters. Finally, our study is also subject to limitations of chart reviews and retrospective studies in general.

This report and other recent studies shed light on a growing epidemic of OPR misuse and associated complications in rural communities in the United States. This report highlights that infectious endocarditis, a severe complication of IDU, has increased in our region along with oral opiate injection misuse. Since IDU is difficult to track from a public health standpoint, infectious endocarditis rates may serve as a useful proxy to identify increased IDU in the community, prompting early public health outreach efforts. Interventions aimed at reducing both the high rates of OPR prescribing and OPR misuse, along with renewed efforts to provide substance abuse counseling and treatment, are needed to combat this profound public health threat.

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FIGURE.

Trends in infective endocarditis and injection drug use. (A) Rates of injection drug use infective endocarditis (IDU-IE) and noninjection drug use infective endocarditis (No IDU-IE) were calculated per 1000 hospital admissions over each quarter year (left y axis). Yearly percentages of IDU-IE to No IDU-IE cases over the study period were calculated (right y axis). The line represents a 4-quarter moving average of IDU-IE to No IDU-IE. (B) Type of drugs that patients reported injecting in the IDU-IE cohort over the study period. The “Other” category included 1 case each of morphine extended release, methadone and cocaine. Some patients reported injecting more than one drug. In 13 subjects with IDU-IE, a specific injection drug was not identified.

TABLE 1

Baseline characteristics.

	IE (<i>n</i> = 127)	IDU-IE (<i>n</i> = 48)	No IDU-IE (<i>n</i> = 79)	<i>P</i> Value
Age	46.1 ± 16.4	32.6 ± 11.7	54.4 ± 13.1	<0.0001
Sex (%male)	87 (68.5%)	32 (66.7%)	55 (69.6%)	0.7283
Race or ethnicity				0.1102
White	112 (88.2%)	46 (95.8%)	66 (83.5%)	
Black or African American	14 (11.0%)	2 (4.2%)	12 (15.2%)	
Latin American or Hispanic	1 (0.8%)	0 (0.0%)	1 (1.3%)	
Marital status				<0.0001
Single	56 (44.1%)	33 (68.8%)	23 (29.1%)	
Married	49 (38.6%)	6 (12.5%)	43 (54.4%)	
Divorced	15 (11.8%)	6 (12.5%)	9 (11.4%)	
Separated	2 (1.6%)	1 (2.1%)	1 (1.3%)	
Widowed	5 (3.9%)	2 (4.2%)	3 (3.8%)	
County type				<0.0001
Rural county	61 (48.0%)	36 (75.0%)	25 (31.6%)	
Nonrural county	66 (52.0%)	12 (25.0%)	54 (68.4%)	

IE, infective endocarditis; IDU, injection drug use.

TABLE 2

Identified bacterial organisms.

	IE (n = 127)	IDU-IE (n = 48)	No IDU-IE (n = 79)	P Value
Microbiology				0.0009
MRSA	14 (11.0%)	6 (12.5%)	8 (10.1%)	
MSSA	27 (21.3%)	19 (39.6%)	8 (10.1%)	
Coagulase-negative staphylococci	9 (7.1%)	0 (0.0%)	9 (11.4%)	
Viridans streptococci	26 (20.5%)	8 (16.7%)	18 (22.8%)	
Enterococcus	16 (12.6%)	3 (6.3%)	13 (16.5%)	
Other streptococci	11 (8.7%)	1 (2.1%)	10 (12.7%)	
Gram-negative rods	3 (2.4%)	2 (4.2%)	1 (1.3%)	
Polymicrobial	5 (3.9%)	4 (8.3%)	1 (1.3%)	
Other ^a	6 (4.7%)	2 (4.2%)	4 (5.1%)	
Unknown	10 (7.9%)	3 (6.3%)	7 (8.9%)	

IE, infective endocarditis; IDU, injection drug use;

MRSA, methicillin-resistant staph aureus; MSSA, methicillin-sensitive staph aureus.

^aOther organisms included *Bacillus cereus*, *Escherichia coli*, *Klebsiella* sp, *Lactobacillus*, *Enterobacter*, *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Candida albicans* and yeast.

TABLE 3

Patient outcomes.

	Median (IQR) or N (%)			P Value
	IE (n = 127)	IDU-IE (n = 48)	No IDU-IE (n = 79)	
Hospital LOS	16.0 (9.0–26.0)	26.0 (17.0–44.0)	12.0 (7.0–19.0)	<0.0001
ICU LOS	1.0 (0.0–4.0)	2.0 (0.0–8.0)	1.0 (0.0–4.0)	0.04
Dialysis				0.49
None	121 (95.3%)	46 (95.8%)	75 (94.9%)	
CRRT	5 (3.9%)	2 (4.2%)	3 (3.8%)	
Dependent on discharge	1 (0.8%)	0 (0.0%)	1 (1.3%)	
Surgery	50 (39.4%)	17 (35.4%)	33 (41.8%)	0.48
Discharge location				0.30
Home	70 (60.9%)	22 (51.2%)	48 (66.7%)	
Skilled nursing facility/LTAC	33 (28.7%)	16 (37.2%)	17 (23.6%)	
Another Hospital	11 (9.6%)	5 (11.6%)	6 (8.3%)	
Hospice	1 (0.9%)	0 (0.0%)	1 (1.4%)	
Hospital mortality	12 (9.4%)	5 (10.4%)	7 (8.9%)	0.77

IE, infective endocarditis; IDU, injection drug use; LOS, length of stay; ICU, intensive care unit; CRRT, continuous renal replacement therapy; LTAC, long-term acute care.