



Original Article

Clinical characteristics and outcome of infective endocarditis among intravenous drug abusers in India



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ABSTRACT

Introduction: Infective endocarditis (IE) is the most dreaded complication of intravenous drug abuse (IVDA). IVDA is present in significant proportions in India. Since there is scarcity of Indian data on IVDA associated IE, we report a study comparing IVDA to non IVDA associated IE. We compare differences in clinical profile, microbiology, echocardiography and clinical outcome from a tertiary care hospital.

Methods: A total of 133 patients admitted from 1st January 2017 to 31st December 2019 who met the Modified Duke “definitive” criteria for IE were included. Detailed Information was collected regarding demography, clinical data and laboratory investigations. All patients underwent transthoracic echocardiography and trans-oesophageal echocardiogram wherever necessary.

Results: Among a total of 133 patients, 54 patients (40.6%) were iv drug abusers. Patients in IVDA-group were younger, mostly males, more likely to have concomitant HCV and HIV infections compared to non IVDA-group. Chronic comorbidities such as DM and CKD were more common in non IVDA-group. Rate of positive blood culture was higher in IVDA-group compared to non IVDA-group (74.1%v/s 32.9%, $p < 0.001$) with different microbiological profile. Percentage of Methicillin resistant staphylococcus aureus (42.6%v/s 17.7%, $p = 0.003$) and pseudomonas related IE (18.5%v/s 2.5%, $p = 0.003$) was significantly higher among IVDA-group. IVDA-group most commonly had tricuspid valve involvement Whereas mitral and aortic valve were most commonly involved valve in non IVDA-group. Mortality was slightly higher among IVDA-group compared to non IVDA-group, though statistically non-significant. Left sided valve involvement and Congestive heart failure were independent predictors of mortality.

Conclusion: IVDA-IE is a significant problem in India. Demographic, microbiological and echocardiographic profile is quite different in IVDA and non IVDA-group. There is urgent need to conduct larger studies.

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1. Introduction

Infective endocarditis (IE) is primarily the infection of endocardium of heart affecting mainly heart valves. IE is still associated with very high morbidity and mortality despite various advances in diagnostic and treatment modalities.

There are various risk factors such as pre-existing valvular disease, congenital heart disease, intracardiac devices such as

permanent pacemakers, prosthetic heart valves and surgical procedure related bacteraemia which predispose to IE.¹ Intravenous drug abuse (IVDA) is an important risk factor as reported in various western studies.^{2,3} There is scarcity of Indian data on IVDA associated IE (IVDA-IE). This is due to the fact that the problem of IVDA among our population has been considered to be small in previous Indian studies.^{4,5} On the contrary, recent surveys show that IVDA is a significant problem in India specifically Punjab. According to a report published in 2019 by the ministry of social justice and empowerment, government of India, there are estimated 8.5 lakh intravenous drug abusers in India and Punjab has the second highest number among all the states.⁶ The Punjab Opioid

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Dependence Survey has also found drug abuse to be a significant problem and has estimated the number of opioid dependent individuals in Punjab to be around 2.32 lakh and approximately one third of these individuals use intravenous (iv) route.⁷ In fact actual number is projected to be even higher.

Since there is limited data on IVDA-IE from India, we are reporting the study comparing IVDA to non IVDA-IE. We compare differences in clinical profile, microbiology, echocardiography and clinical outcome from a tertiary care referral hospital.

2. Methods

This study was carried out in a super specialty tertiary care referral hospital. This was an ambispective study including all the patients admitted with diagnosis of IE. Patients who met the Modified Duke “definitive” criteria for IE were included.⁸ Patients with possible IE were excluded. Patients were recruited retrospectively ($n = 31$) during the period from 1st January 2017 to 30th June 2018 and prospectively ($n = 102$) from 1st July 2018 to 31st December 2019. Retrospective data was obtained from the clinical records confirmed with investigations record obtained from echocardiography and microbiology department. Detailed Information was collected regarding demographic data, clinical data, and laboratory investigations including blood cultures. Transesophageal echocardiogram (TEE) was performed in patients with non-diagnostic TTE, suspected prosthetic valve endocarditis (PVE) and suspected cardiac mechanical complications.

The study was approved by the institutional ethical committee.

2.1. Statistical analysis

Data has been expressed as mean \pm SE for quantitative variables and as frequency (%) for qualitative variables. Fisher exact test or Chi-square test was applied for comparison of categorical variables. *t*-test was applied for comparison of mean values. $p < 0.05$ was considered statistically significant. Univariate logistic regression analysis was carried out to assess the odds of factors associated with mortality. Variables which showed higher odds of mortality ($p < 0.05$) in the univariate analysis were included as independent variables for multivariable logistic regression analysis. Statistical analysis was conducted using Microsoft excel and windows based SPSS software (version 17.0).

3. Results

Baseline characteristics and predisposing conditions are shown in Table 1. Among a total of 133 patients, 54 patients (40.6%) were iv drug abusers. When comparing patients with IVDA to those without IVDA, they were younger. They were more likely to have concomitant HCV and HIV infections (Table 2). Other chronic comorbidities such as DM and CKD were more common in non-IVDA group. 98.1% of patients in IVDA-group were males as compared to 63.3% in non-IVDA group.

More than 50% of patients in non-IVDA group had predisposing cardiac conditions which were unlikely in IVDA group. Invasive procedure related infective endocarditis was also common in non IVDA group.

Microbiological findings are shown in Table 2. Rate of positive blood culture was higher in IVDA compared to non IVDA group (74.1 v/s 32.9%, $p < 0.001$). Causative microbiological agent differed significantly among two groups, as shown in Table 2.

Percentage of Methicillin resistant staphylococcus aureus (MRSA) related IE was significantly higher in IVDA compared to non IVDA group. Pseudomonas IE was also more common among IVDA

compared to non IVDA group. Interestingly, none of our patients grew streptococcus viridians in blood culture.

Echocardiographic and laboratory findings are shown in Table 3. Multiple vegetations were observed in 5.3% of patients. IVDA group most commonly had tricuspid valve (TV) involvement compared to non IVDA group. Whereas mitral valve (MV) was the most commonly involved valve in non IVDA group compared to IVDA group.

There were no significant differences in terms of multi-valvular involvement, intra-cardiac complications (abscess perforation) and embolic events among two subgroups except for pulmonary infarct which was more common among IVDA group (Table 4).

Mortality was slightly higher among IVDA group compared to non IVDA group, though statistically non-significant (22.2% v/s 17.7%, $p = 0.520$). Recurrent admissions (≥ 2 admissions) and need of surgery were also similar in two groups.

Table 5 shows regression analysis (univariate and multivariate) for predictors of mortality. Univariate analysis showed that Left sided valve involvement (MV, Aortic valve or both) had higher odds of mortality [odds ratio (OR) 3.39, 95% CI: 1.09–10.58; $p = 0.028$] compared to right sided valve involvement [TV, pulmonary valve (PV) or both]. Patients with congestive heart failure (CHF) were also at higher odds of mortality (OR 2.73, 95% CI: 1.14–6.56; $p = 0.037$). Both Left sided valve involvement ($p = 0.008$) and CHF ($p = 0.003$) were also independently associated with mortality on multivariate analysis also. Pseudomonas IE was associated with higher mortality on univariate analysis (OR 0.19, 95% CI: 0.06–0.68; $p = 0.013$) but adjusted odds ratio on multivariate analysis was not significant ($p < 0.05$).

4. Discussion

Drug addiction and IVDA is present in significant portions in our country.^{6–7} Punjab is currently worst hit as large number of youths in productive age group of 18–35 years are affected. IVDA impacts all the aspects of health adversely, accounting for significant morbidity and mortality. IE is the most dreaded complication of IVDA. But IVDA-IE has never been reported in previous Indian studies. Since there is scarcity of Indian data, we are reporting a study on various aspects of IVDA-IE from a tertiary care referral centre. This study also compares IVDA with non IVDA-IE to shed light on differences in baseline characteristics, predisposing conditions, microbiology, echocardiographic patterns and outcomes from a tertiary care center in the current era.

Mean age of our population was 38.08 ± 14.73 years which is relatively young compared to most studies from developed countries.^{9,10} Most Indian studies from non IVDA-IE also reported a younger age of presentation which was primarily attributed to higher incidence of RHD.^{1,11–14} Whereas in the current study, young age of presentation is due to the fact that 40.6% of our subjects are iv drug abusers which afflicts mainly young population. Mean age was significantly lower among IVDA compared to Non IVDA-IE. Patients in IVDA-group were mostly males, more likely to have concomitant HCV and HIV infection. Similar observations have been reported from western literature also.^{2,3,15} A retrospective study from United States using national inpatient sample registry (2002–2016) found that patients in IVDA group were younger (median age, 38 versus 70 years; $p < 0.001$) and more commonly males (55.5% versus 50.8%; $p < 0.001$) compared to non IVDA group. They also had higher proportion of concomitant HCV and HIV infection.³

Among predisposing conditions, IVDA-IE accounted for 40.6% of cases which underpins the threat of drug abuse that looms over Indian population. Other predisposing conditions were uncommon and majority of the cases among iv drug abusers occurred in structurally normal valves. RHD accounted for only 9.0% of cases in

Table 1
Baseline characteristics, predisposing conditions and comorbidities according to drug abuse status.

BASELINE CHARACTERISTICS	Total population(n = 133)	IVDA group (n = 54)	Non IVDA group(n = 79)	p VALUE
Age(years)	38.08 ± 14.73	29.39 ± 7.85	44.01 ± 15.41	<0.001
Male sex	103 (77.4%)	53 (98.1%)	50 (63.3%)	<0.001
HUMAN IMMUNODEFICIENCY VIRUS	3 (2.3)	3 (5.6)	0	0.065
DIABETES MELLITUS	20 (15.0)	0	20 (25.3)	0.000
CHRONIC KIDNEY DISEASE	7 (5.3)	0	7 (8.9)	0.041
PREGNANCY	1 (0.8)	0	1 (1.3)	0.407
HEPATITIS C VIRUS	34 (25.6)	28 (51.9)	6 (7.6)	<0.001
MALIGNANCY	1 (0.8)	0	1 (1.3)	0.407
PREDISPOSING CONDITIONS				
In hospital infection	5 (3.8)	0	5 (6.3)	0.080
Invasive procedure-related ^a	23 (17.3)	1 (1.9)	22 (27.8)	<0.001
MITRAL VALVE PROLAPSE	9 (6.8)	1 (1.9)	8 (10.1)	0.083
BICUSPID AORTIC VALVE	4 (3.0)	0	4 (5.1)	0.146
degenerative Aortic valve disease	10 (7.5)	0	10 (12.7)	0.006
RHEUMATIC HEART DISEASE	12 (9.0)	1 (1.9)	11 (13.9)	0.027
VENTRICULAR SEPTAL DEFECT	3 (2.3)	1 (1.9)	2 (2.5)	0.795
Device related (PACEMAKER/AICD ^b)	2 (1.5)	0	2 (2.5)	0.239
Prosthetic valve	6 (4.5)	0	6 (7.6)	0.081

Values are in mean ± SD or n(%).

^a Preceding Dental procedure, gynaecological procedure, central venous catheters.

^b AICD: automated implantable cardioverter defibrillator.

total population and 13.9% among non IVDA group. This is in contrast to Indian studies which attribute majority of cases (40–70%) to RHD.^{12–14} This is likely because of declining incidence of RHD in our country.^{16–18} MVP accounted for 6.8% of total cases and 10.1% cases among non IVDA. Similar incidences (3.1–10%) have been reported from other Indian studies.^{1,12,19}

Blood culture positivity rate was low (49.6%) in our study. In another Indian study, culture positivity rate was only 41%. Prior use of antibiotics has been considered an important reason for low culture positivity. Failure to culture fastidious organisms is another possible reason. Such a low culture positivity rate akin to various other Indian studies is worrisome as it affects the choice of antibiotics and limits treatment to empirical therapy which may be responsible for higher morbidity & mortality in our patients.^{1,20,21}

Interestingly, culture positive rate was higher in IVDA group compared to non IVDA group. Reasons for this observation are not clear. Repeated iv injections leading to higher degree of bacteraemia and less use of prior antibiotics due to avoidance of treatment by drug abusers may be the possible explanations. Also non IVDA group had significant associated chronic comorbidities which may make them susceptible to nontraditional/fastidious organisms which are difficult to culture.

Staphylococcus aureus has emerged as the most common cause of IE worldwide.²² The same was observed in our study also. It was the most common organism among both the groups. *Pseudomonas* was fairly common being responsible for 18.5% of cases among IVDA which is a novel finding. This incidence is higher than that published previously in both IVDA & non IVDA-IE.^{3,23} None of our patient was positive for viridans streptococci. Most plausible reason is prior use of antibiotics but changing microbiological pattern worldwide may also be responsible. This needs to be evaluated in future studies.

For the clear reasons, IVDA-IE most often involved TV as has been seen in majority of other reports on IVDA-IE. Various mechanisms responsible are direct injury of TV by injected particulate matter, use of unsterile syringes and needles, drug mediated physiological change that yield vasospasm and cardiac injury.²³

Damage caused by IVDA was not restricted to TV only. MV & AV involvement was also common and seen in 22.2 and 9.3% of IVDA-IE. This is partly because the most common causative microbes (MRSA and *Pseudomonas*) are highly virulent and affect normal as well as left sided valves too. In a multicenter prospective cohort study, Munoz et al reported that MV and AV were involved in significant number of cases (26.9% and 25% respectively) among

Table 2
Microbial isolates according to drug abuse status.

	Total population(n = 133)	IVDA group (n = 54)	Non IVDA group(n = 79)	p VALUE
Viridans group streptococci	0	0	0	
Streptococcus agalactiae	1 (0.8)	0	1(1.3)	0.407
Enterococcus faecalis	4 (3.0)	1(1.9)	3(3.8)	0.646
MRSA ^a	37 (27.8)	23(42.6)	14(17.7)	0.003
MSSA ^b	4 (3.0)	3(5.6)	1(1.3)	0.303
Coagulase negative Staphylococcus	0	0	0	
HACEK ^c	0	0	0	
Fungi	3 (2.3)	2(3.7)	1(1.3)	0.566
E.coli/klebsiella	4 (3.0)	1(1.9)	3(3.8)	0.646
Pseudomonas	12 (9.0)	10(18.5)	2(2.5)	0.003
Achromobacter xylosoxidans	1 (0.8)	0	1(1.3)	0.407
Culture positive	66 (49.6)	40(74.1)	26(32.9)	<0.001
Culture negative	67 (50.4)	14(25.9)	53(67.1)	<0.001

Values are in n(%).

^a Methicillin-resistant *Staphylococcus aureus*.

^b Methicillin-sensitive *Staphylococcus aureus*.

^c Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella.

Table 3
Echocardiography and Laboratory Findings according to drug abuse status.

	Total population(n = 133)	IVDA group (n = 54)	Non IVDA group(n = 79)	p VALUE
ECHOCARDIOGRAPHIC FINDINGS				
Mitral valve ^a	55 (41.4)	12(22.2)	43(54.4)	<0.001
Aortic valve	30 (22.6)	5(9.3)	25(31.6)	0.003
Tricuspid valve	47 (35.3)	37(68.5)	10(12.7)	<0.001
Pulmonary valve	1 (0.7)	0	1(1.3)	0.407
Multivalvular involvement	7 (5.3)	1	6	0.240
Prosthetic valve	6 (4.5)	0	6	0.081
LABORATORY FINDINGS				
Low Hemoglobin (<12 gm%)	114 (85.7)	47 (87)	67 (84.8)	0.719
Raised ESR (≥20 mm)	112 (84.2)	49 (90.7)	63 (79.7)	0.088
Leucocytosis (>11,000/mm ³)	92 (69.2)	43 (79.6)	49 (62)	0.036
Leucopenia (<4000/mm ³)	2 (1.5)	0	2 (2.5)	0.239
Thrombocytopenia	43 (32.3)	24 (44.4)	19 (24.1)	0.015
Microscopic Haematuria	18 (13.5)	7 (13)	11 (13.9)	0.874
Elevated CRP	73 (54.9)	30 (55.6)	43 (64)	0.156
Positive rheumatoid Factor	3 (2.3)	0	3 (3.8)	0.147
Fever >38 C	130 (97.7)	53 (98.1)	77 (97.5)	0.795

Values are in n(%).

^a Total number of all valves combined exceeds the total number of subjects because of multivalvular involvement.

Table 4
Complications and outcome according to drug abuse status.

	Total population(n = 133)	IVDA group (n = 54)	Non IVDA group(n = 79)	p VALUE
Intracardiac complications(abcess/perforation)	8 (6.0)	2(3.7)	6(7.6)	0.472
Ischemic Stroke	11 (8.3)	4(7.4)	7(8.9)	0.765
Embolisation, non stroke	26 (19.6)	14(25.9)	12(15.2)	0.125
Intracranial hemorrhage	3 (2.3)	0	3(3.8)	0.147
New onset conduction abnormality	5 (3.8)	0	5(6.3)	0.117
Pulmonary infarct	12 (9.0)	9 (16.7)	3 (3.8)	0.014
Duration of stay (days)	14.4 ± 11.6	15.7 ± 14.5	13.6 ± 9.2	0.31
Surgery	15 (11.3)	4 (7.4)	11 (13.9)	0.243
Recurrent admissions(≥2 admissions)	33 (24.8)	14 (25.9)	19 (24.1)	0.806
Mortality	26 (19.5)	12(22.2)	14(17.7)	0.520

Values are in mean ± SD or n(%).

Table 5
Univariate and multivariate logistic regression analysis for factors associated with mortality (n = 26).

Variable	Frequency(%)	Odd ratio (95% CI)	p-value	Adjusted Odd ratio (95% CI)	p-value
Age (Mean ± SD)	35.62 ± 15.34	0.98 (0.95–1.01)	0.344	–	–
Left sided valve involvement ^a	21 (84)	3.39 (1.09–10.58)	0.028	6.03 (1.62–22.53)	0.008
Leucocytosis (>11,000/mm ³)	19 (73.1)	1.26 (0.48–3.29)	0.631	–	–
Deranged renal Function test	14 (53.8)	1.74 (0.73–4.1)	0.207	–	–
Deranged liver Function test	12 (46.2)	2.20 (0.92–5.29)	0.075	–	–
Congestive heart failure	14 (53.8)	2.73 (1.14–6.56)	0.037	5.13 (1.74–15.14)	0.003
Septic pulmonary infarct	2 (7.7)	0.81 (0.16–3.94)	0.792	–	–
septicemia	22 (84.6)	2.56 (0.82–8.01)	0.097	–	–
Intracardiac complications	2 (7.7)	1.40 (0.26–7.38)	0.688	–	–
Intra venous drug abuse	12 (46.2)	0.75 (0.32–1.79)	0.520	–	–
MRSA ^b	7 (26.9)	1.26 (0.48–3.29)	0.631	–	–
Pseudomonas	6 (23.1)	0.19 (0.06–0.68)	0.013	2.95 (0.77–11.23)	0.113
Multivalvular involvement	1 (3.8)	1.48 (0.17–12.90)	0.718	–	–
Surgical treatment	0	–	0.042	Went out of equation	–
Ischemic Stroke	4 (15.4)	2.59 (0.69–9.65)	0.224	–	–

^a Mitral valve, aortic valve or both.

^b Methicillin-resistant *Staphylococcus aureus*.

Spanish intravenous drug abusers.²⁴ In non IVDA-IE, MV and AV were most commonly involved. TV involvement was less common. This is similar to reports from various Indian & western studies.^{1,11–14,23}

Out of various complications, pulmonary infarct was more common in IVDA-IE because of obvious reasons of pulmonary embolization of septic material from TV.

Overall mortality in our population was 19.5% with slightly higher mortality in IVDA (22.2%) compared to non-IVDA group (17.7%). This is considerably higher than western reports.^{3,25} In a recent study, IDVA-IE was associated with 6.8% index hospitalisation mortality.²⁵ Also there was significantly less mortality (9.6%) among Non IVDA-IE in that study which is significantly less than our study. In our study, Higher mortality may be due to sicker

patients, delay in seeking treatment and higher culture negativity rate. Higher frequency of virulent organisms such as pseudomonas may also be responsible.

On multivariate analysis, Left sided endocarditis and CHF were found to be independent predictors of mortality. This is in accordance with other reports which show that the mortality in left sided endocarditis is higher as compared to right sided endocarditis.^{3,25} Increased mortality in left sided endocarditis may be due to systemic embolization and CHF. It is well known that occurrence of CHF during the course of IE portends a bad prognosis.¹⁹

To conclude, IVDA-IE is a significant problem in India associated with very high morbidity and mortality. The current study highlights important clinical, microbiological & echocardiographic aspects of IVDA-IE from India. Since there is limited data on IVDA-IE due to lack of Indian studies, there is a dire need to conduct larger prospective studies especially in regions with high IVDA incidence.

4.1. Study limitations

Our study has a few limitations. Firstly, it was a single center study. Being from a tertiary care center, the study also suffers from inherent referral and selection bias. Hence it may not represent the actual scenario in general population. We did not use any advanced serological and molecular technique for microbiological diagnosis.

Conflicts of interest

All authors have none to declare.

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