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Infective endocarditis and intravenous drug use: an observational study.

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Background

Intravenous drug use (IVDU) is a recognised predisposition for the development of infective endocarditis (IE). The incidence of IE is increasing in the UK and globally[1,2], and the aetiology has shifted with an increase in IVDU[3]. The UK has the highest rates of IVDU in Europe[2].

Previous studies of surgery in this group have been of variable size and the duration of follow-up has often been short[4-6]. These studies have mainly compared outcomes in IVDUs with non-IVDUs.

The European Society of Cardiology (ESC) guidelines defines the following as Class I indications for surgery for left sided disease as[7]:

Heart failure
Aortic or mitral valve IE causing severe regurgitation/obstruction/fistulation.
Leading to either refractory pulmonary oedema, cardiogenic shock, symptoms of heart failure or echocardiographic evidence of poor haemodynamic tolerance

Uncontrolled infection
Locally uncontrolled infection, such as abscess, fistula, enlarging vegetation or false aneurysm.
Infection caused by fungi or multi-resistant organism.

Prevention of embolism
Aortic/mitral IE with persistent vegetation >10mm after one/more embolic episodes during appropriate antimicrobial therapy.

In clinical practice, these indications are extrapolated to the right heart to justify surgery where pulmonary embolization or severe regurgitation occurs.

Controversy

Despite ESC guidelines being clear on Class I indications for surgery[7], poor compliance with medical therapy, poor long-term outcomes in this sub-group as well as re-infection risks associated with ongoing IVDU are concerns that can delay surgery[6,8].

A particular problem is encountered when patients who have had valve surgery re-present with a second episode of endocarditis which has resulted from continued drug use.

Aims

We aim to describe the characteristics, complications and outcomes of IVDUs with IE reviewed by the local endocarditis team at the Leeds Teaching Hospitals NHS Trust (LTHT) over more than a decade.

The focus is to understand the role of surgery for IE in IVDUs and how this affects outcomes for these patients, and whether re-infection rates and long-term outcomes should influence decision making regarding surgery.

Ethical considerations

This study was submitted to the Research and Innovation Department at LTHT. It was regarded as a service evaluation and therefore did not require specific ethical approval or patient consent providing usual data protection was in place.

Conflicts of interest statement

There are no conflicts of interest for any of the authors.

Study design

The design was an observational study based on a prospectively collected database.

Patients

Consecutive patients admitted between 01/01/06 and 31/12/16 referred to the local endocarditis team with suspected IE were eligible for inclusion.

Inclusion in the study was dependent on the modified Duke criteria. For an episode to be eligible we required:
- Duke definite

OR
- Duke possible and treated by the local endocarditis team as IE

AND
- Predisposing IVDU (within 90 days)

Data collection

This dataset was derived from a local database of all cases referred to the local endocarditis team. For each patient the written medical record was reviewed alongside local electronic patient records.

The following information was obtained:
Patient characteristics
- Age
- Sex
- Severity of illness (qSOFA score on admission)

IE variables
- Affected structures
- Microorganisms (blood and cultures of excised valves)

Complications
- Heart failure (peripheral or pulmonary congestion, with echocardiographic evidence of haemodynamic dysfunction)
- Embolisation
- Abscess formation

Surgery
- Type of operation(s)
- Number of operations
- Indication for operation.

Outcomes

Reinfection
- **Relapse** – reinfection with same pathogen within 1-year
- **Recurrence** – reinfection with different pathogen OR reinfection with same isolate beyond 1-year

Repeat surgery
All-cause mortality

Episodes

During the study period there were:
- 109 episodes
- 92 patients
- 95 episodes Duke definite
- 14 episodes Duke possible and treated for IE

Affected structures

IE affected left-sided structures more than right.

Figure 1. Frequency of left and right sided episodes of IE

In 15 episodes more than one structure was involved. A pacemaker infection occurred in one patient.

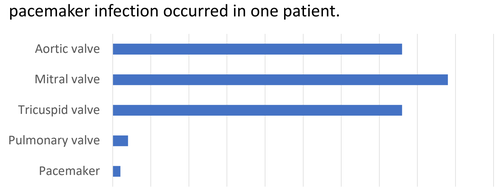

Figure 2. Frequency of structures affected during episodes of IE

Microorganisms

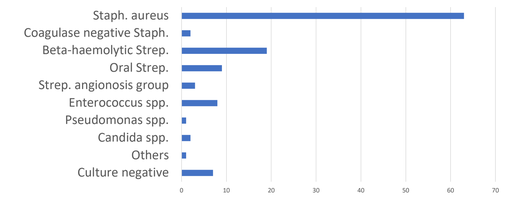

Figure 3. Frequency of microorganisms identified..

- *Staph. aureus* was the most common pathogen and occurred in 57.8% of episodes.
- 7 episode were culture negative
- 7 episodes involved two pathogens

Complications

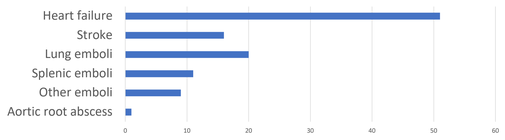

Figure 4. Frequency of complications.

Other emboli included: renal, mesenteric, endophthalmitis, upper and lower limbs.

Significant complications were common in this cohort and occurred in 68.8% of episodes. These were discussed at the cardiac surgery MDT for their suitability for operation.

Surgery

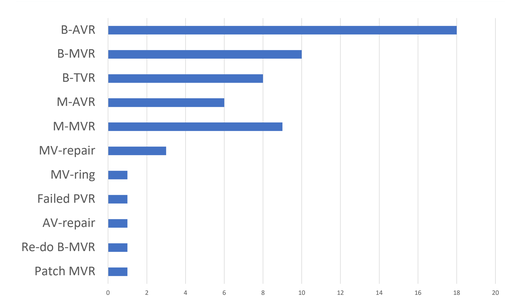

Figure 5. Frequency of type of operation.
M, mechanical; B, bioprosthetic; AVR, aortic valve replacement; MVR, mitral valve replacement; TVR, tricuspid valve replacement; PVR, pulmonary valve replacement.

49 patients (53.3%) underwent surgery. In all cases there was a Class I indication for surgery.

Implantation of bioprosthetic valves for left-sided disease was the most common intervention. Intervention on right sided structures was uncommon. There was one abandoned attempt at pulmonary valve replacement.

Only one patient underwent a second operation during the study period due to late recurrence with *S. epidermidis.*

There were no significant differences in the pre-specified characteristics of those who were operated on compared to non-operated except a preponderance of left-sided disease (table 1).

	Operated (n=49)	Non-operated (n=43)	*p* value
Age (years)	37.2 (8.3)	36.1 (8.7)	0.53
Male sex	31 (70.5)	33 (70.2)	1.00
S. aureus	23 (52.3)	30 (63.8)	0.37
Left sided	28 (63.6)	20 (42.6)	
Right sided	6 (13.6)	24 (51.1)	
Both	10 (22.7)	3 (6.4)	**<0.001**
qSOFA ≥ 2	5 (13.9)	7 (17.9)	0.87

Table 1. Characteristics of operated compared to non-operated group

Cardiac re-infection

- Recurrence rate 13.0%
- Relapse rate 3.26%

In this group outcomes were poor,. At follow-up 8 had died. The causes of death were heart failure (3), sepsis (3), stroke (1) and bronchopneumonia(1). The clinical state of the patient often meant that they were unsuitable for repeat surgery when this might have been considered.

Survival

	1 year	3 years	5 years	10 years
Overall	73.6	61.9	58.7	43.4
Operated	68.2	52.5	46.3	29.3
Not operated	78.7	71.2	71.2	55.1

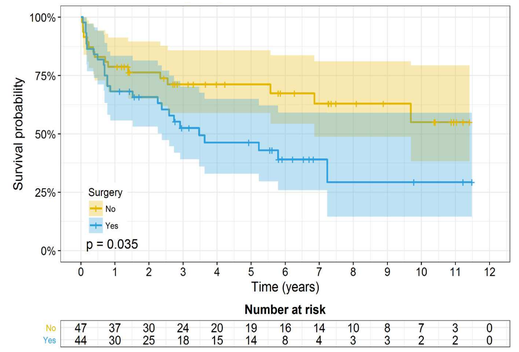

Figure 6. Kaplan Meier survival curves for operated and non-operated groups.

In the operated group, short term mortality was low. However, this was not translated into long term survival. The survival in the surgical group was <30% at 10 years (figure 6).

In regression analysis the odds of mortality were increased with surgery, qSOFA ≥2 and were lower with right sided infection (table 2).

	Univariable model	Multivariable model
Operated	1.96 (1.04-3.69)	1.83 (0.79-4.26)
Age (years)		1.06 (1.01-1.12)
Male sex		0.74 (0.32-1.69)
S. aureus		0.42 (0.19-0.91)
Left-sided		1
Right-sided		0.46 (0.16-1.36)
Both		0.22 (0.05-1.04)
qSOFA <2		1
qSOFA >=2		2.96 (1.05-8.36)

Table 2. Regression analysis of covariables and their association with mortality

On review of the medical records, the majority of deaths occurred late and were unrelated to an episode of IE. Compliance with anticoagulation is an important consideration, however there was no evidence that this contributed to late mortality (figure 7). Those offered mechanical valves in fact faired better, but this relationship was not statically significant and the numbers at risk were small.

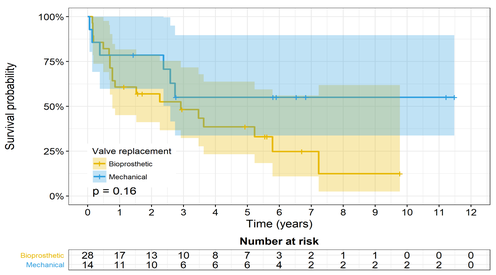

Figure 7. Kaplan Meier survival curves for mechanical or bioprosthetic valves.

Discussion

Contrary to common perception, IE affected left-sided structures more commonly than right. There may have been inclusion bias as LTHT receives patients from local hospitals, most of whom require surgery. However, our data are consistent with other contemporary studies[5,6].

Long-term survival following an episode of IE was low in this cohort. Most of the deaths were unrelated to a further episode of IE. When compared to the medically treated group, survival was reduced in the surgical cohort. The reasons for this are not immediately obvious but were not related to choice of prosthesis. However, the survival curves were similar despite surgery being indicated by significant complications.

30-day mortality and relapse rates were low which indicates that we were mostly successful in treating the acute episodes. IVDU patients are known to have significantly reduced life expectancy compared to age and sex-matched controls[9]. The high all-cause mortality which we report suggests that a proportion of patients continue to lead a high-risk lifestyle. Continued IVDU after completing treatment is a recognised problem. We did not measure the rate of return to IVDU but a recent study found that 70% and 44% of patients returned to IVDU following a first and second operation, respectively[6].

The rate of cardiac re-infection was low but these patients had a high mortality rate. In this patient group, those who might have been eligible for re-operation were often too unwell to be considered for surgery. There was a preference to treat recurrent right-sided infection conservatively and these patients survived.

Surgery was performed for Class 1 indications. It seems probable that the majority of these patients would have died in the short-term, if not operated on as a consequence of severe heart failure, embolization or uncontrolled sepsis. Surgery was successful in all but one episode but predicted life expectancy was often not achieved.

Surgery can redress haemodynamic and embolic problems but it is important to remember the need for an holistic approach in managing this challenging patient group after they have completed their acute treatment. We hypothesise that the continued high mortality in this patient group is part of the spectrum of complications related to chronic drug misuse.

References

1. Yew, H.S. and D.R. Murdoch, *Global trends in infective endocarditis epidemiology.* Curr Infect Dis Rep, 2012. **14**(4): p. 367-72.
2. Eurosurveillance editorial, t., *The European Monitoring Centre for Drugs and Drug Addiction publishes the European Drug Report 2013: trends and developments.* Euro Surveill, 2013. **18**(22).
3. Beynon, R.P., V.K. Bahl, and B.D. Prendergast, *Infective endocarditis.* BMJ, 2006. **333**(7563): p. 334-9.
4. Shetty, N., et al., *Surgical and Medical Management of Isolated Tricuspid Valve Infective Endocarditis in Intravenous Drug Users.* J Card Surg, 2016. **31**(2): p. 83-8.
5. Kim, J.B., et al., *Surgical outcomes of infective endocarditis among intravenous drug users.* J Thorac Cardiovasc Surg, 2016. **152**(3): p. 832-841 e1.
6. Osterdal, O.B., et al., *Cardiac surgery for infective endocarditis in patients with intravenous drug use.* Interact Cardiovasc Thorac Surg, 2016. **22**(5): p. 633-40.
7. Habib, G., et al., *2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM).* Eur Heart J, 2015. **36**(44): p. 3075-128.
8. Wahba, A. and D. Nordhaug, *What are the long-term results of cardiac valve replacements in left sided endocarditis with a history of i.v. drug abuse?* Interact Cardiovasc Thorac Surg, 2006. **5**(5): p. 608-10.
9. Ghodse, A.H., et al., *Deaths of drug addicts in the United Kingdom 1967-81.* Br Med J (Clin Res Ed), 1985. **290**(6466): p. 425-8.