PostOPerative AnTIbiotic MAnagement Duration FoLlowing Surgery for IVDA Endocarditis (OPTIMAL)

NCT05156437

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Protocol Number & Study Protocol Title

PostOPerative AnTIbiotic MAnagement Duration FoLlowing Surgery for IVDA Endocarditis (OPTIMAL)

Abbreviations List

IVDA: Intravenous Drug Abusers
IV: Intravenous

Section I: Team and Research Summary

Study Team Composition

Principal Investigator *– Vinay Badhwar, MD*
Co-Investigator(s) *– ; J. Hunter Mehaffey, MD;J. Awori Hayanga, MD; Arif Sarwari, MD; Lawrence Wei, MD, Joy Juskowich, MD, : Kimberly Quedado, PhD; Joshua Bombard, MS*

Research Summary

Study Population *N=20 subjects*
Inclusion:

- *The age of the patient is ≥ 18.*
- *The patient has undergone an urgent or emergent primary cardiac valvar operation as treatment for IVDA endocarditis, with blood cultures positive for Streptococcus, Enterococcus faecalis, Staphylococcus aureus, coagulase-negative Staphylococci, or gram-negative organism with susceptibility to an oral antimicrobial with high bioavailability*
- *The patient has received 2 weeks of postoperative inpatient IV antibiotic therapy with negative blood cultures and no residual active infection by imaging (i.e. computerized axial tomography, echocardiography)*
- *The patient has the capacity to participate in a compliance tracking tool for medication administration (e.g. a centrally managed core site mobile Medisafe compliance https://www.medisafe.com/) as confirmed by both a physician and a care management team member*

Exclusion:

- *Inability to give informed consent*
- *Residual infection requiring IV antibiotic therapy*
- *Any persistent secondary noncardiac infection (e.g. infections of solid organs or joints)*
- *Known poor compliance or deemed incapable to comply with the compliance tracking tool*
- *Reduced absorption or inability to receive oral treatment due to a gastrointestinal disorder*
- *Endocarditis attributed to fungal organisms.*
- *Cancer not otherwise in remission or in need of current or future oncologic therapy*
- *Medically immunocompromised state*
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- *History of habitual noncompliance*
- *Pregnancy*
- *Mental incapacity*
- *Unable to perform local or institutional medical and psychiatric follow up*
- *Unstable home environment*
- *Inadequate access to mobile cell service (geographic/rurality)*

***Study Design** – Prospective randomized institutional pilot trial of 20 subjects.*

Both groups will receive the following support:

1. *All patients will enroll in aggressive drug rehabilitation with mandatory participation in a formal psychiatric rehabilitation program for a minimum of 6 weeks (combined inpatient and outpatient),*
2. *All patients will be followed closely by Infectious Disease specialists*
3. *All patients will undergo monitoring of treatment efficacy with serum antibiotic levels during the treatment phase*
4. *All patients will undergo surveillance monitoring of treatment efficacy with blood cultures, and*
5. *All patients will participate in a compliance tracking tool for medication administration (e.g. a centrally managed core site mobile Medisafe compliance program [https://www.medisafe.com/]. All patients and their family/primary care givers receive Medisafe compliance training).*

***Patients:** Postoperative patients who have undergone valvar repair or replacement for IVDA endocarditis may be prospectively randomized into two arms:*

1. *Group I (Experimental Group): 2 weeks of postoperative inpatient IV antibiotic therapy followed by 4 weeks of oral therapy with outpatient follow-up.*
2. *Group II (Control Group): conventional 2 weeks of postoperative inpatient IV antibiotic therapy followed by 4 weeks of IV antibiotic therapy (inpatient or facility supervised if indwelling catheter utilized).*

Subjects will be identified by the study investigators and research coordinators. Once inclusion and exclusion criteria have been met, the patient will be approached by the primary investigator and/or study investigator to present the study. If the patient indicates interest in the study, the study investigator will collaborate with the research coordinator to obtain informed consent.

***Study Duration** – Subjects will be followed for twelve (12) months. Enrollment is expected to take one (1) year to achieve our proposed sample size. Data collection will occur in real-time throughout the study and data analysis will be performed at the conclusion of the study.*

Section II: Design

Background & Significance

The US opioid epidemic has been implicated in substantial rises in mortality, morbidity, and costs. According to the Centers for Disease Control and Prevention, between 1999 and 2017 there were nearly 218,000 opioid-related deaths in the US, 47,600 in 2017 alone.[1] The staggering rise in recent years is illustrated by a 9.6% increase in the age-adjusted rate of overdose deaths just from 2016 to 2017.[1] States with the highest rates of death due to drug overdose, the majority from intravenous (IV) heroin use, were West Virginia (57.8 per 100,000), Ohio (46.3 per 100,000), Pennsylvania (44.3 per 100,000), the District of Columbia (44.0 per 100,000), and Kentucky (37.2 per 100,000).[1, 2, 3] The increasing rate of drug overdose death has been accompanied by a commensurate increase in the incidence of IV drug–associated (IVDA) acute infective endocarditis.[4]

The clinical impact of the opioid crisis can be demonstrated by the exponential rise in the incidence and costs associated with IVDA endocarditis. Given the ongoing societal problems with access, addiction, and recidivism, the secondary epidemic of IVDA endocarditis presents a substantial operational, ethical, and financial challenge for health systems and physicians providing essential care for these patients.

The current management of acute IVDA endocarditis is associated with unique challenges. Operations are often urgent or emergent due to associated acute secondary hemodynamic embarrassment. Operative complexity is often increased due to multivalve or intracardiac abscess involvement. Postoperative challenges include the need for additional noncardiac procedures, the use of indwelling catheters to deliver prolonged parenteral antibiotics to patients addicted to IV drugs, and the need for ample time for detoxification and addiction counseling to prevent recidivism. Despite the widely held perception that peripherally inserted central catheters are less morbid than traditional central lines, their complication profiles are not dissimilar and life-threatening problems can occur.[5] The management and cost of the appropriate use of indwelling peripheral catheters in IV drug–abusing patients is not trivial. Following successful complex valve operations, patients with incompletely or untreated addiction discharged with these catheters for prolonged IV antibiotics may be often complicated by acute recidivism and early postoperative mortality. For this reason, many institutions have recently adopted a policy of inpatient management until the IV antibiotic course is complete. This prolonged hospitalization period provides time for detoxification, transition from postoperative narcotic pain management to partial opioid antagonists such as buprenorphine for addiction maintenance, and commencement of a crucial component of inpatient drug rehabilitation.[6] This ethically and medically sound policy has an impact on healthcare costs that is unstainable, however. Moreover, once patients have recovered from a successful operation, the addiction and social issues that led to IV drug abuse may remain. These issues may be significant, because many patients refuse further treatment and sign out of the hospital against medical advice. It is not uncommon for patients to bargain to leave the hospital and even to request permission to take oral antibiotics and attempt to enroll in an inpatient drug rehabilitation program closer to home.

Early transition to oral antibiotic therapy in the postoperative management of endocarditis may provide several advantages. Should this be found to be safely applicable to postoperative IVDA endocarditis patients, these benefits may be further compounded. Advantages include a reduction in catheter-related complications, decreased LOS, an earlier return to normal function, and reduced cost. Should an increase in compliance be facilitated with simpler oral administration, this would facilitate earlier intensive addiction counseling and drug rehabilitation. Of course, such an option might not be appropriate for all patients with IVDA endocarditis, such as those in whom secondary noncardiac infection may persist (solid organs or joints), or for those with endocarditis attributed to fungal organisms.

Objectives

Purpose *– The purpose of this post-operative institutional pilot trial is to ascertain the safety and compliance of initial IV antibiotic followed by oral therapy following uncomplicated IVDA endocarditis. Endocarditis has a high rate of morbidity and mortality, involves prolonged hospitalization and prolonged use of IV antibiotics necessitating six (6) weeks of in-patient stay, and comes with a high cost.*

Primary Objective *– To assess all-cause mortality, recurrent blood culture positive infection, or cardiac re-operation at six (6) months and twelve (12) months.*

Secondary Objective(s) *– To assess all-cause mortality, readmission for recurrent infection or cardiac re-operation, and cost at six (6) and twelve (12) months.*

Rationale*: The key principle of this hybrid pathway (regional or smaller scale trial) is to focus on both "implementation science" and "effectiveness":*

- ***Effectiveness****: This study will document that in postoperative patients who have undergone valve repair or replacement as treatment for IV drug–associated (IVDA) endocarditis:*

- *Will ascertain safety and compliance for 2 weeks of postoperative IV antibiotics followed by 4 weeks of oral antibiotics versus 6 weeks of conventional postoperative IV antibiotics*
- ***Implementation science**: This study will document that patients managed with either arm of the protocol can achieve compliance with and graduation from a drug rehabilitation program. The implementation science portion of this trial will place particular emphasis on the measurement of compliance (e.g. a centrally managed core site mobile Medisafe compliance program [https://www.medisafe.com/]).*

Study Design & Methodology

This is a prospective pilot post-operative institutional study to ascertain safety and compliance of initial IV antibiotic followed by oral therapy following uncomplicated IVDA endocarditis. Data will be collected to ascertain safety and compliance of initial IV antibiotic followed by oral therapy following uncomplicated IVDA endocarditis.

There may be no direct benefit to study participants, but this research will make a significant contribution to the scientific field and general population. Future studies that can further inform the care of these subjects can be built upon the results from this study.

Target Population & Recruitment Methods

Prospective randomized institutional pilot trial of 20 subjects. This is a pilot post-operative institutional trial to ascertain safety and compliance therefore sample size is adequate.

***Study Population** N=20 subjects*
Inclusion:

- *The age of the patient is ≥ 18.*
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Patients: *Postoperative patients who have undergone valvar repair or replacement for IVDA endocarditis may be prospectively randomized into two arms:*

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Subjects will be identified by the study investigators and research coordinators. Once Inclusion and Exclusion criteria have been met, the patient will be approached by the primary surgeon and/or study investigator to present the study. If the patient indicates interest in the study, the study investigator will collaborate with the research coordinator to obtain informed consent.

Study Duration *– Subjects will be followed for twelve (12) months. Enrollment is expected to take one (1) year to achieve our proposed sample size. Data collection will occur real-time throughout the study and data analysis will be performed at the conclusion of the study.*

Risk & Benefit

Risk *– Subjects may experience recurrence, lack of infection resolution, and/or adverse drug reaction.*

Benefit – *Subjects may be free from hospitalization sooner and have a reduced risk of catheter-related bloodstream infection.*

Statistical Analysis Plan

Sample Size *– Prospective randomized institutional pilot trial of 20 subjects. This is a pilot post-operative institutional trial to ascertain safety and compliance therefore sample size is adequate. Appropriate statistical analyses will be conducted such as T-tests, ANOVA, correlations, linear and logistic regression.*

Data Safety Monitoring *– Specify whether there will be a safety data monitoring plan implemented for the project. This is an ongoing review of the study, actions, data collection, and analysis throughout the entirety of the project.*

A Data Safety Monitoring Committee will be formed with clinicians within the Heart & Vascular Institute and Department of Medicine, Section of Infectious Disease as well as a biostatistician consult. Data will be reviewed at when N=1 subjects are enrolled into each arm, again when N=4 are enrolled into each arm, and then again at the end of the study.

Safety Monitoring & Unanticipated Event Reporting

The study investigators along with the research coordinator will monitor data collected on subjects. If there are any events of concern, the research coordinator will work with the study investigators to assess the event and determine the next steps for adjudication and reporting, if applicable.

Study Duration & Timeline

Subjects will be followed for twelve (12) months. Enrollment is expected to last one (1) year. Data collection will occur real-time throughout the study and data analysis will be performed at the conclusion of the study.

Section III: Informed Consent Process

Informed Consent Process

Subjects will be identified by the study investigators and research coordinators. Once Inclusion and Exclusion criteria have been met, the patient will be approached by a study investigator to present the study. If the patient indicates interest in the study, the study investigator will collaborate with the research coordinator to obtain informed consent.

Confidentiality & Privacy

Confidentiality *– All data collected will be kept for 3 years after the conclusion of the study. Any physical copies of data collected will be locked in a drawer or file cabinet, within a locked room or office. Digital data will be encrypted or on a password protected database/drive. All participant identifiers will be stored separately from the data collected.*

Privacy *– Conversations with subjects will be conducted in the privacy of their hospital room. Data kept safe and secure according to the process explained above.*

Section IV: Other Considerations

Conflict of Interest

No conflict of interests to report.

References

Correctly reference any material that was presented in the background, or used to formulate the hypothesis, study objectives, and/or design of the research. These should be in a format that is generally accepted in your field of study.

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