Title: Effect of Oral and Intravenous Diltiazem Protocol for Emergency Department Atrial Fibrillation

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Introduction or Background

Atrial Fibrillation (AF), a supraventricular tachyarrhythmia, is the most common sustained cardiac arrhythmia (Nileshkumar et al., 2014). The number of hospitalizations yearly for AF is increasing progressively from 312,926 in the year 2000, to 409,854 in 2010, with a total of 3,960,011 hospitalizations for AF reported in the United States over that same time period (Nileshkumar et al., 2014). In 2005, the total cost for the treatment of non-valvular atrial fibrillation was estimated at 6.65 billion dollars (Coyne et al., n.d.). Further, the prevalence of AF has been projected to increase to 15.9 million by the year 2050 with more than half of these patients ≥80 years of age (Nileshkumar et al., 2014). Considering all of these factors, the total economic burden and public health concern regarding AF is of increasing significance, therefore it is important to determine effective treatment strategies that can help reduce hospital admissions, costly ICU admissions, and length of stay.

There are two approaches to managing AF in the emergency department (ED): rate control and rhythm control. The AFFIRM trial in 2002 found no significant survival advantage in rate vs rhythm control strategies. Rate control was associated with less adverse drug effects and hospitalizations (Wyse et al., 2002). The RACE II trial in 2010 established that less aggressive rate control (110 bpm) was as effective in preventing adverse cardiovascular events as strict control (80 bpm) (Van Gelder et al., 2010). Beta blockers and non-dihydropyridine calcium channel blockers are accepted rate controlling agents. Emergent treatment of stable AF with rapid ventricular response (RVR) in the ED should aim to achieve lenient heart rate control for improved patient outcomes to reduce side effects while providing equal treatment outcomes.

Problem and Purpose Statement-Objective of the Research

The primary objective of this study is to reduce hospital admissions and decrease time to disposition through establishing an effective treatment protocol for AF and Atrial Flutter in the Emergency Departments of Spectrum Health Lakeland. Additionally, there is a secondary outcome to be measured. Is oral Diltiazem (a non-dihydropyridine calcium channel blocker) an effective HR controlling agent in AF RVR and Flutter. Currently, treatment of AF can be performed with multiple drugs and formulations, resulting in different dispositions from the ED. Previous studies have shown that ED AF observation is an effective strategy that can reduce admissions and time to disposition. (WW et al., 2008) In 2018 researchers at VCU retrospectively compared heart rate control with oral Diltiazem vs. continuous IV infusion of Diltiazem. Their study exhibited that oral Diltiazem was as effective in HR control for AF RVR, with less treatment failures. (Means et al., 2018) We hope to add to the supportive data for using oral Diltiazem for heart rate control in AF RVR or Flutter. An oral one-time medication administration would reduce strain on nursing staff, medication costs, and decrease disposition time. Improving efficient and effective treatment of AF in the ED.

Throughout the Spectrum Health Lakeland System in 2018 - 68.5% of patients with a primary diagnosis of AF were admitted to the hospital, the cost of care for these patients was nearly 16.5 million dollars. Of AF patients who presented to Spectrum Health Lakeland, 8% were observed from the emergency department for a total cost of 1.27 million dollars. Is it possible that some of those admitted patients could have been observed, and discharged more expediently while reducing healthcare costs?

Research Questions or Hypothesis

Below are the 2 main research hypotheses that we aim to test.

1. Instituting an ED AF observation treatment protocol will reduce admissions and time to disposition in observation.

2. Oral Diltiazem is an effective heart rate controlling agent for AF RVR in the ED

Theoretical Framework-Present Knowledge /Literature Review

The RACE and AFFIRM trials have shown that rate control is as effective, and a potentially safer, treatment for AF RVR than electrical or chemical cardioversion (JL and RE, 2003). The RACE II trial has also shown that lenient HR control with HR <110 is as effective as strict control HR<80, and easier to achieve (Van Gelder et al., 2010). Accepted rate controlling agents include Metoprolol, Diltiazem, and Digoxin. Metoprolol and Diltiazem are often chosen for treatment of AF with RVR, given as intravenous boluses or infusions. They have been shown to have no statistical difference in their ability to achieve rate control, with a similar adverse effect profile (Hirschy et al., 2019). Traditionally, patients are treated with an initial IV bolus of medication followed by an infusion or additional IV pushes until HR is achieved. After heart rate goal is achieved, they are transitioned to oral medications, and observed until deemed stable for discharge. An observation protocol for AF can reduce time to disposition and admissions as shown in a study published in Annals of Emergency Medicine in 2008 (WW et al., 2008). This study had inclusion criteria of <48hrs of symptom onset, and also included electrical cardioversion as a possible endpoint. There have been other published protocols for AF RVR observation that displayed decreased admission rates, but there is also a focus on optional cardioversion (Koenig et al., 2002). The RACE, RACE II, and AFFIRM trials have shown that lenient HR control is a safe and equally effective treatment modality for AF RVR, regardless of time of onset.

Diltiazem is a non-dihydropyridine calcium channel blocker useful in the management of AF in the absence of pre-excitation (Ganz, n.d.). In the ED, acute rate control using Diltiazem is accomplished with a loading dose, given as an IV infusion, plus or minus a second dose given after 15 minutes if there was not a 20 percent reduction in heart rate from the baseline, or a heart rate less than or equal to 100 BPM after the initial dose (Ganz, n.d.). Individuals who respond to the first or second bolus can be initiated on a continuous infusion of IV Diltiazem or be given PO immediate release tablets for continued management of heart rate. Patients who are treated with oral Diltiazem require less resources, given that IV continuous infusion patients must have their dose frequently titrated by nursing. Oral Diltiazem with ED observation has the potential to effect overall visit healthcare costs and length of stay. A 2018 VCU retrospective study found that PO immediate-release Diltiazem was associated with a lower rate of treatment failure (sustained heart rate >110 beats/min at four hours or conversion to another agent) as compared to IV continuous infusion Diltiazem in patients with AF with RVR (Means et al., 2018). However, no study has yet to be completed implementing oral Diltiazem treatment uniformly amongst patients presenting in AF with RVR. We aim to test the external validity of the 2018 VCU study and add to the data on oral Diltazem as a rate-controlling agent for AF RVR.

A new ED observation unit at SHL has been built with hopes to be up and running in 2020. AF will be one of the conditions treated in this new unit. To ensure all patients receive excellent and efficient care, the oral Diltiazem AF RVR protocol will be instituted as the AF treatment protocol.

Methodology

Patients will be entered into the protocol from the ED if they are deemed to meet the inclusion criteria specified below. The St. Joseph and Niles Emergency Departments will be used to enroll participants. Patients who meet criteria will be transferred to the observation unit and will receive the treatment protocol listed below. The treatment protocol will be explained to them by the ED Physician or Resident responsible for their care. Nurses and techs using the Phillips monitors in each patient room will collect data and enter it into the Epic EHR. HR and BP will be recorded as listed below in the order set for the protocol. The outcome of rate of treatment success defined as HR <110 at 4 hours post study entry (as was defined in the 2018 VCU study) will be measured. (Means et al., 2018) This will be compared with data from the 2018 study at VCU using chi-squared test. Additional outcomes including length of stay from time of arrival in the ED to discharge from the observation unit, and admission rates will be recorded. Admission rates and length of stay will be compared to historical data from Lakeland.

This data will be maintained only upon Lakeland severs and computers.

Time to discharge can be compared to retrospective means from 2018-2019 using students t-test. This data will be gathered from Epic EHR for AF patients treated at either emergency department participating in the study. Admission rates will be analyzed using chi-squared testing. We will gather this data from time of study start in 2020 to that exact date in 2021. ED return visits within <72hrs will be recorded. Patient characteristics including age, sex, race, and weight will also be gathered. Deidentified data will ultimately be sent to the SASS group at Spectrum in GR for statistical analysis.

Research Design- Proposed Observation Protocol

This includes AF Protocol formatted as an Orderset which will contain orders for data gathering, medications, and patient care- to be selected in EPIC.

Atrial Fibrillation Observation Treatment Protocol – Orderset

Use ED to Obs AF Protocol if patient meets the following inclusion criteria.

Inclusion Criteria:

Patient is stable, HR>110 with Systolic BP>100, afebrile, Atrial Fibrillation/Flutter confirmed on ECG. Meets observation unit requirements (performs certain ADLS), Age>18. If patient has history of Atrial Fibrillation and takes rate controlling/anti-arrhythmic agent please still use observation Diltiazem protocol. If unstable cardiovert.

Exclusion Criteria:

WPW, STEMI, Pregnant, Sepsis, Decompensated HF, allergy to Diltiazem, provider discretion

Start with ED order set, when completed use observation order set when admitting to observation.

ED Orderset – Use First

Meds:

Diltiazem 0.25mg/kg injection, give over 2 minutes, max dose 30mg (Ross et al., 2016).

15 minutes following Diltiazem Infusion administer oral Diltiazem 60mg IR Tablet, do not give if BP<100

Labs:

Thyroid Function Cascade

Comprehensive Metabolic Panel

Complete Blood Count-w/ Diff

Magnesium

PT

PTT

High Sensitivity Troponin Initial – If indicated/Provider Discretion

Imaging/ECG

12 Lead ECG

Chest Xray AP/PA one view

Nursing:

Prior to Starting Diltiazem Infusion- Obtain HR, BP, and RR

-1st Hour following Diltiazem Infusion 15min Vitals HR/BP

-Hourly post Diltiazem Infusion- HRx3 1 minute apart, BP

- Insert peripheral IV

-Cardiac telemetry class II

-Continuous pulse oximetry

Obs Orderset – Use Second

Admit to Observation order, place in bed for observation services emergency medicine, provider

Diet-General

Code status order

Oxygen Therapy Per Protocol: Routine, PRN to maintain SpO2>92%

Nursing Care

Nursing interventions

UNTIL DISCONTINUED, Notify provider for pulse less than 60 or greater than 150, respiratory rate less than 12 or greater than 25, temperature greater than 38.5, urinary output less than 30 mL/hr for four hours, systolic BP less than 90 or greater than 180, diastolic BP less than 60 or greater than 90.

Notify provider if HR>130 at 2hour mark post Diltiazem Infusion (Provider consider starting IV infusion/medication change)

Notify Provider if HR<110 for >1hr at any time- patient may be ready for discharge

Vital Signs

-Hourly post PO Diltiazem- HRx3 1 minute apart, BP - continued from ED set

Cardiac telemetry class II

Continuous pulse oximetry

Nursing to call cardiology for follow up appointment. Goal for appointment to be made within 3 days

Activity as tolerated

Medications

IV fluids

0.9% NS Infusion- provider discretion

325mg Aspirin PO- if suspected ACS

Assessments:

Chads2Vasc Calculator:

Age <65-0, 65-74-+1, >75 +2

Sex Male-0, Female-+1

CHF history Yes +1. No-0

HTN History Yes+1, No-0

Stroke/TIA/Thromboembolism History- Yes+2, No-0

Vascular Disease History (Prior MI, PAD, Aortic Plaque)

Diabetes History- Yes +1, No-0

Score of 0-1 – no anticoagulation indicated, consider daily 81mg Aspirin

2+- Anticoagulation indicated- start Eliquis

Anticoagulation for Discharge

Eliquis- 5mg BID (unless age≥80, weight ≤60kg, Creatinine ≥1.5mg/dL, then reduce dose to 2.5mg BID) (ZA and SK, 2018)

If patient has mechanical heart valve and not anti-coagulated, start on Coumadin with dosing below. Also, start if patient has known moderate/severe mitral stenosis. 5mg x 3 days- INR check morning of day 4

If frail, elderly (eg, woman >70 years, man >80 years), malnourished, has liver or kidney disease or heart failure, or is receiving a medication known to increase warfarin sensitivity (eg, Amiodarone) - 2.5mg x 3days INR check day 4

Perform Lovenox bridging 1mg/kg Subcutaneous daily until INR check. Give first dose prior to discharge. (Ha et al., 2017)

Order 1mg/kg Lovenox Daily, route Subcutaneous

Discharge order 1mg/kg Lovenox Daily, route subcutaneous X 4 days

Imaging

Cardiac Transthoracic Echo – if patient has not had echo in last 6 months. Indication Atrial Fibrillation

Consult: Cardiology- Reason Atrial Fibrillation

On call provider – *Optional -Concern for ACS, chest pain

Discharge:

If patient does not require further CPU management/Cardiology Evaluation and does not require admission discharge if HR is <100, SBP>100

Discharge patient with proper anticoagulation based on above. If already on rate controlling agent assess reason for elevated HR. If appropriate, resume home rate controlling agent or make dosage adjustment. Phone consult to cardiology if change in agent considered.

If no prior rate controlling agent, discharge with 120mg ER PO Diltiazem tab- Once Daily. Give prior to discharge.

All patients need cardiology/PCP follow up preferably within 3 days – Nursing make appointment prior to discharge

End of Protocol and Orderset

Consent/Ethical Considerations

Since this is a new observation protocol that all patients treated for AF in the ED will receive, patients will not be signing consent. The treatment will be explained to them by the ED physician or resident providing their care. As stated previously by the RACE II trial, lenient rate control is not inferior

to strict rate control in management of AF. It resulted in a 12.9% rate of cardiovascular morbidity as defined by a composite of death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. Strict rate control had a rate of 14.9% $p<0.001$. (Van Gelder et al., 2010). Lenient rate control is achieved with Diltiazem, Metoprolol, or Digoxin traditionally. As stated earlier, Diltiazem and Metoprolol both effectively achieve HR control (Hirschy et al., 2019). The 2018 study at VCU exhibited that PO diltiazem was associated with treatment success (HR<110 @ 4hrs) vs. IV Diltiazem infusion. Therefore, patients entered into the AF observation protocol will be receiving accepted medications and treatment strategies effective for AF with RVR. In fact, the American College of Emergency Physicians guidelines recommends an IV Diltiazem bolus followed by PO Diltiazem as an optional treatment protocol for AF RVR (Baugh et al., 2018). Patients are not required to sign consent when treated with antibiotics for an infection or analgesics for a headache. Consent is not then required to partake in the protocol. As stated previously, all patient data will be kept on SHL computers and servers only. Deidentified data will be given to the statistical analysis team.

All patients that meet the criteria for the AF observation protocol will be entered. There is no placebo group or alternate interventions. When considering risk, any medication or medical procedure carries with it some inherent risk but, in the case of atrial fibrillation with a rapid ventricular response, the potential benefit of said therapy is thought to outweigh the risk. The possible side effects of Diltiazem include: an allergic reaction, blistering/red skin rash, nausea, vomiting, dizziness, loss of appetite, stomach pain, a fast, slow, uneven, or pounding heartbeat, rapid weight gain, or swelling in the hands, ankles, or feet. The incidence of side effects is generally low and usually from <1% to 10% depending on the reaction (UpToDate). As outlined above the patient's will be monitored for possible adverse effects while under observation in the emergency department with cardiac monitoring, pulse oxymetry monitoring and regular measurements of vital signs (including heart rate and blood pressure). Patients with significant CHF or autonomic instability who are not diagnosed or new onset may have increased risk for hemodynamic complications. These patients should be excluded by the exclusion criteria, vitals, and clinical history, but it is possible for a patient who should be excluded to be given the treatment.

We do not predict there will be any breaches of confidentiality, however when working with electronic databases, there is always a small possible risk for loss of confidentiality. Efforts will be made to limit a patient's personal information, including research study and medical records, to people who have a need to review this information. Raw data will be maintained electronically only upon Lakeland servers and computers. De-identified data may be sent to the SASS group at Spectrum for statistical analysis. Organizations that may inspect and copy the information for quality assurance and data analysis include: the investigators and their research staff, Spectrum Health Lakeland staff or its agents, the Spectrum Health Lakeland Institutional Review Board (IRB) and staff, the Sponsor(s) of the research or its agents (monitors, auditors) and/or agencies that accredit the hospital or the research program.

Benefits of the study include that participation may help us to better understand the most effective treatment option for atrial fibrillation in the emergency department setting and reduce health care costs associated with the treatment of this diagnosis. This study will generate no additional costs to patients but patients will still be responsible for the payment of their standard treatment. It is possible that individuals who undergo ED observation with treatment as opposed to hospital admission will be discharged more expediently, thereby reducing their personal healthcare costs as well.

There will be no recruitment materials, advertisements or press releases as part of this study. No surveys, questionnaires or other research instruments will be used.

Monitoring

We will review an Epic report of patients who utilized the protocol on a monthly basis to assess for hypotensive episodes.

Statistical Analysis Plan

The initial data containing the demographics and medications contained 1745 unique individuals. This number decreased to 1106 unique individuals after filtering out patients who did not receive medication. Then, the four medication variables in the main spreadsheet were looked through and observations were dropped or placed in their group accordingly. This resulted in 363 patients in the treatment group (87 of whom needed rescue meds) and 549 patients in the comparison group for a total of 912 patients.

The heart rate spreadsheet contained 1524 unique patients. Only 1089 of these patients had heart rate data. 712 patients remained after filtering for an initial heart rate above 110. When the two spreadsheets were merged, many patients either did not have medication given (from heart rate spreadsheet) or their heart rate monitored (from demographic spreadsheet). This caused additional observations to be dropped. The hours from the first medication administered for each patient was calculated. Patients were only included in the analysis if any heartrate measurements were recorded between 2-4 hours of the first medication being given. If their heartrate fell below 110 at any point during that time period, the treatment was considered a success.

There were 444 patients left to analyze after cleaning and filtering the data. The treatment group had 177 patients (55 of whom needed rescue meds) and the comparison group had 267 patients. Demographic data and the initial vital signs were compared across treatment groups. Treatment success was also determined and compared at the 3 ± 1 hour mark.

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