Title: A comparison of PLAtelet response to Aspirin between emergency department patients with chest pain receiving Fentanyl or Morphine (PLAAFM)

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Introduction or Background

Problem and Purpose Statement-Objective of the Research

The aim of this project was to determine whether fentanyl and morphine have similar effects in reducing aspirin's effect upon platelets in emergency department patients with chest discomfort. Morphine has been shown to worsen outcomes in heart attack patients due to reduction of oral anti-platelet agent effectiveness and so many providers have switched to using fentanyl. However, it is largely unknown whether fentanyl has similar effects.

Theoretical Framework-Present Knowledge, Literature Review

Patients experiencing heart attacks or unstable angina (commonly known as acute coronary syndrome (ACS)) commonly experience discomfort and pain. Nitroglycerin is typically the first medicine given for discomfort because it has dilatory effects upon vasculature to reduce the blood pressure and relax blood vessels to decrease myocardial demand. However, in some patients it is contraindicated and in many patients it is only partially efficacious in reducing discomfort. Narcotics are commonly given. Classically morphine was given in ACS as it is also thought to have venodilatory properties and could perhaps also relax the patient to decrease the sympathetic demands of the fright-fight-flight responses experienced by patients having heart attacks. Narcotics have several common side effects, and one of these is decreased gastrointestinal (GI) transit time, commonly manifested as constipation. However, this decreased GI transit time also can slow the absorption of oral medications. Oral anti-platelet therapy (starting with aspirin and commonly including dual anti-platelet therapy with clopidogrel as well) is also part of the treatment of patients with ACS as reducing clot propagation in the coronary arteries can decrease the size of an infarct. Interference with oral anti-platelet therapy has been observed with morphine (2) contributing to worse outcomes in patients receiving morphine (1). Delayed onset of action or decreased absorption has also been demonstrated with stronger anti-platelet drugs such as clopidogrel (3) and prasugrel (4) in association with morphine. Many physicians have therefore switched to using fentanyl, and fentanyl has been found to be equally efficacious in pain control in potential ACS (7). The PACIFY trial (5) evaluated the effects of fentanyl upon the stronger anti-platelet agent ticagrelor and found statistical significance at 2 hours with a lower peak concentration, and delayed onset of the peak concentration of ticagrelor when fentanyl was given. The PACIFY trial did not compare the effects of morphine to fentanyl. The PERSEUS trial was a small study of 38 patients (6) which showed no difference between fentanyl and morphine at 2 hours with regards to ticagrelor absorption but that there was a difference at 4 hours. There has not to our knowledge been any study of fentanyl's effect on aspirin absorption.

Research Questions or Hypothesis

It is unlikely that a sufficient sample of patients with acute coronary syndrome (ACS) can be obtained to prospectively compare fentanyl to morphine, as the administration of other anticoagulants would confound the results. Therefore, the study will focus on chest pain patients in the emergency department. The hypothesis is that both morphine and fentanyl will reduce the effectiveness of aspirin.

Methodology

Given the challenges in obtaining a sufficient sample of patients with acute coronary syndrome (ACS) to prospectively compare fentanyl to morphine, the study will focus on chest pain patients in the emergency department. These patients typically have blood drawn initially and again two hours later to check for elevation and changes in troponin levels, a cardiac muscle protein detectable when cardiac muscle is being injured. These blood draws will be supplemented by evaluating platelet aggregation at the 0 and 2-hour marks.

There are many measures and techniques in evaluation of platelet function. Light Transmission Aggregometry (LTA) looks at changes in light transmittance through serum as platelets aggregate, leading to increased light transmission as more platelets aggregate. Aspirin interferes with arachidonic acid mediated aggregation because of its effects upon COX-1 conversion of arachidonic acid to thromboxane A2. Arachidonic acid is therefore the best trigger to use to evaluate aspirin's effect upon platelets, as opposed to epinephrine, ADP, or several others used to evaluate the stronger anti-platelet oral and IV agents that act in different places in the platelet activation cascade (8).

Research Design
Patients who have 0 and 2 hour troponins ordered will have their chart reviewed by the research coordinator for candidacy in the study (see below for inclusion/exclusion). If the patient meets study entry criteria then platelet aggregation studies using arachidonic acid will be added on to the 0 and 2 hour lab draw.

The study will compare the 0 and 2-hour platelet aggregation scores of patients receiving aspirin who are undergoing two sets of troponin tests. The first group will consist of patients not receiving any narcotics, the second group will include those receiving morphine, and the third group will include those receiving fentanyl. The treating clinician will determine the appropriate pain treatment plan for each patient.

Sample/Participants
The research coordinator will perform chart review on Emergency Department patients presenting with chest discomfort. If there are 2 sets of troponins ordered and no exclusion criteria then the research coordinator will approach the patient for consent.

Inclusion criteria: Adult Emergency Department patients undergoing 0 and 2 hour troponin testing who have been administered aspirin within 30 minutes of the initial blood draw. Initially all patients undergoing this testing will be candidates for the study. We will attempt to enroll 80 patients in the each of the 3 arms. Determination of which (if either) narcotic is administered will be up to the clinician. As we reach the enrollment goals our research coordinator will discuss with the clinicians the expected pain plan to tailor enrollment of patients in the treatment arms that are still needed

Exclusion criteria: Patients not expected to get a 2 hour troponin; patients already on aspirin, clopidogrel, or stronger anti-coagulants; patients who arrived via EMS given it can be difficult to find the run reports to determine whether patient received fentanyl in the pre-hospital period; pregnant patients; patients on chronic narcotics; patients already once enrolled in this study, inability to provide consent in English

With regards to at risk populations, Economically Disadvantaged, Nursing home residents, prisoners, homeless patients are all commonly encountered in the ED. However, the request of 1 or 2 blue top tubes (totaling about a teaspoon of blood) is not an onerous ask. Since narcotic use (or non-use) will be wholly up to the provider and not impacted by this study we see no problems with including them.

Setting-Where is this taking place?

Emergency Department in St Joseph.

Instrumentation-Data collection
If consent is given to obtain the labs then the research coordinator will extract basic demographic information into a spreadsheet (name, MRN, age, sex, race, ethnicity), as well as the results of the labs including the CBC data already obtained (hemoglobin and platelet count). We will record the patients' creatinine to also help describe our population. Finally the platelet aggregation data that we are studying will be recorded, as well as confirmation with the patient that they are not on anti-platelet medicines such as aspirin, clopidogrel (Plavix), aspirin-dipyridamole (Aggrenox), prasugrel (Effient), ticagrelor (Brilinta). We will record time and dosing of aspirin administration, time and dosing of narcotic medicines (morphine, fentanyl, dilaudid).

This spreadsheet would be maintained on SH-Lakeland servers in a location only accessible to the research coordinator and PI.

Ethical Considerations
There are not significant risks to this study. Two blue-top tubes of blood will be required for this study. One is already drawn and generally discarded as part of the initial rainbow of blood that's drawn. 2.7ml of blood is used to fill a blue top tube, a trivial amount. Because these labs are not used clinically, we will seek grant funding to cover these expenses.

Because this study does not pose risks we make no plans for injury compensation. This blood test is approved for research purposes only and is not used for clinical decision making so we are not concerned about incidental findings with regard to potential outlier values.

The aim of this study is to provide better understanding of commonly used medicines' potential for unintended consequences.

Procedures
The duration of participation is limited to the two blood draws.

Data Analysis Procedure
In the PACIFY trial, at 2 hours, patients receiving fentanyl had a PRU value of 113 +/- 94 on the platelet aggregation study (light aggregometry using ADP) after receiving Brilinta (ticagrelor), versus 71 +/- 66 in those not receiving fentanyl. With an alpha of 0.05 and beta of 0.8, 57 patients would be required to demonstrate statistical significance if there is a similar magnitude of effect. In the PERSEUS trial at 2 hours, patients receiving fentanyl had a PRU value of 173 +/-90 after also receiving Brilinta (ticagrelor), versus 210 +/- 76 in those receiving morphine and Brilinta (ticagrelor). 74 patients would be required to show statistical significance in direct comparison of morphine vs fentanyl. The aim is to enroll 80 patients in each arm (no narcotic, morphine, and fentanyl).

Two-tailed T-testing will be used to look for differences in the 2 hour platelet reactivity response rates between those receiving morphine versus those not receiving narcotics and between those receiving fentanyl and those not receiving narcotics.

If the data is sent to the Spectrum Health SASS team for analysis MRN's will be converted to a study ID so that the actual MRN will not be sent out.

References

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