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Assessing the Safety of Buprenorphine in People With Sickle Cell Disease
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JHM IRB - eForm A – Protocol

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1. Abstract

Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

There are only a few therapies available to decrease vaso-occlusive crisis (VOC) in people with sickle cell disease; stem cell transplant, chronic transfusion therapy and hydroxyurea. Most recently L-glutamine has been FDA approved but it is reserved for only a small subset of people with the disease. Transplant is the only known cure for this disease. Its safety and efficacy, especially in adults, remains a concern and is only available to adults as a research protocol. Chronic transfusion therapy is an effective way of decreasing the risk of several complications of SCD including stroke and VOC events. Hydroxyurea is an effective disease-modifying therapy that decreases the risk of VOC by 50%. However, neither chronic transfusions nor hydroxyurea have been shown to decrease the intensity of chronic pain. There is a subset of patients who are on effective disease modifying therapy, yet continue to have frequent acute visits for parenteral opioids and are maintained on high dose oral opioids as outpatients.

Buprenorphine is a partial mu-agonist and kappa antagonist and has a very high affinity for the mu receptors, with an elimination half-life of 28-37 hours for the sublingual administration. The lower risk for misuse, diminished withdrawal symptoms and cravings for opioids as well as the reduced risk of overdose in this drug make it an appealing alternative to full agonist opioid use in a subset of patients with sickle cell disease on who are unable to wean off of opioids.

Most relevant to SCD patients on high doses of opioids, there has been recent data on successful conversion for patients with chronic pain who are on high-dose opioids, from 100mg to 400mg morphine equivalents, to SL buprenorphine. This study reported a decrease in pain scores after the initiation of SL buprenorphine therapy for more than two months. Our goals of this study is to assess patient important outcomes post conversion to buprenorphine.

2. Objectives

The purpose of this study is to assess the safety and benefit of converting adults with sickle cell disease on high dose opioid therapy with evidence of opioid use disorder to buprenorphine. The primary outcome will be to assess the safety of the protocol. Secondary outcomes will include measures of acute care utilization and health related quality of life after conversion.

Primary Endpoint: This will be a descriptive study assessing the safety and benefit of converting subjects from full agonist opioids to buprenorphine. Data will be collected on need for hospitalization within 72 hours of conversion due to withdrawal induced VOC, as well as average COWS scores.

Secondary Endpoint: Measurement of quality of life, decrease in pain measured by the BPI and Promis pain tools decrease acute care utilization. In addition we will collect data from the 15-20 patients that have

already been converted to buprenorphine as part of routine care to formally examine utilization pre and post conversion.

3. Background

Sickle cell disease (SCD) is a genetic disorder of the hemoglobin that leads to severe morbidity and early mortality. It is the most common disease detected by newborn screening efforts in the United States (U.S.) [1]. Between 80,000 and 100,000 individuals in the U.S. are affected by some form of SCD [2]. African-Americans (AA) are most affected in the U.S., as 1 per every 400 AA newborns is born with the disease. There are several genotypes that lead to similar phenotypes in SCD. Those who are homozygote for the sickle mutation (SS) have the most severe form of the disease and typically make up 60-70% of those with sickle cell disease. People with SC disease are compound heterozygotes and are considered to have a milder phenotype but there is a wide spectrum and chronic pain is quite prevalent in people with SC disease often due to avascular necrosis of the hips and shoulders. The damage SCD inflicts on sufferers is dramatic. The disease reduces life expectancy by approximately 30 years compared to the general population [3]. Furthermore, the disease limits quality of life - as severely as does end-stage renal disease requiring hemodialysis [4].

The best-known complication of SCD is the vaso-occlusive crisis (VOC). These acute, excruciatingly painful events are the leading cause of hospital and emergency department utilization [5], and can be associated with such lethal and disabling complications as acute chest syndrome and stroke. Triggers for the development of VOC include intravascular volume depletion, stress and infection. In addition to these acute episodes of pain, the prevalence of chronic pain is very high [6], [7]. Acute and chronic pain and disease severity contribute to extraordinarily high levels of unemployment, and decreased productivity in this patient population. Therefore, the persistent balance of pain control and quality of life remains a challenge.

The mechanisms of chronic pain in SCD are poorly understood. A number of factors ranging from genetic to behavioral likely regulate the pain response in people with SCD and include interactions between the nervous, endocrine, and immune systems [8]. The role of the immune system is of particular interest in understanding pain due to SCD; the role of inflammation in acute painful episodes is currently being explored through clinical trials investigating new treatment modalities. That ongoing inflammation may play a role in chronic pain is suggested by the identification of elevated levels of inflammatory cytokines and substance P, the neuropeptide modulator of inflammation and nociception, in SCD [9]. Additionally, chronic pain resulting from SCD is now hypothesized to be partly a disorder of central sensitization and peripheral neural sensitization. Central sensitization is a complex phenomenon, with contributions from plasticity induced by excitatory amino acids via NMDA receptors [10] and neural changes induced by inflammatory mediators and other nociceptive chemical messengers. To make things more complicated, our group and others have shown that opioid induced hyperalgesia may contribute to chronic pain via central sensitization [11]. A fascinating outcome of successful, curative stem cell transplant is that almost every adult patient reported in the literature who was on chronic opioid therapy prior to transplant was weaned off of those medications post-transplant. This phenomenon, which we have seen in our own transplant population, suggests that bone damage is likely a small component of the chronic pain and raises even more concern that hyperalgesia induced by opioid use itself may be playing a role in the patient experience of chronic pain.

The current standard of care for the treatment of chronic pain in people with sickle cell disease is the use of both long and short acting opiates. Full agonists are opioid drugs that bind completely to mu opioid receptors in the brain, and cause them to produce endorphins which relieve pain [12]. The best approach to the treatment of chronic pain in people with sickle cell disease is unclear and there is little literature on the effectiveness of chronic opioid therapy in this patient population. In a recently published paper we compared pain symptoms in 83 adults who were either on chronic opioid therapy or not. We found that those on chronic opioid therapy exhibited greater levels of clinical pain, central sensitization as well as higher levels of healthcare utilization. This suggested that despite the use of opioid therapy, patients continued to have a very high symptom burden.

As with any persistent use of opiates for other chronic pain conditions, there is an increase probability of opioid dependency and in rare cases, an increased probability of aberrant opioid use. Opioid induced hyperalgesia, central sensitization and refractory pain are potential long-term outcomes for many SCD patients on long term opioids, potentially leading to higher doses of opioids over time [11]. Therefore, there may be great value in reducing the use of full agonist opioids for patients with sickle cell disease.

There are only three therapies available to decrease vaso-occlusive crisis (VOC); stem cell transplant, chronic transfusion therapy and hydroxyurea. Transplant is the only known cure for this disease; its safety and efficacy, especially in adults, remains a concern and is only available to adults as a research protocol. Chronic transfusion therapy is an effective way of decreasing the risk of several complications of SCD including stroke and VOC events [13]. Hydroxyurea is an effective disease-modifying therapy that decreases the risk of VOC by 50%. However, neither chronic transfusions nor hydroxyurea have been shown to decrease the prevalence of chronic pain. There is a subset of patients who are on effective disease modifying therapy, yet continue to have frequent acute visits for parenteral opioids and are maintained on high dose oral opioids as outpatients.

Buprenorphine is classified as a partial mu-agonist and kappa antagonist and has a very high affinity towards the mu receptors, with an elimination half-life of 28-37 hours for the sublingual administration [14]. The lower risk for misuse, diminished withdrawal symptoms and cravings for opioids as well as the safety profile of this drug make it an appealing alternative for full agonist opioid use in a subset of patients with sickle cell disease who are unable to wean off of opioids.

Most relevant to SCD patients on high doses of opioids, there has been recent data on successful conversion for patients with chronic pain who are on high-dose opioids, from 100mg to 400mg morphine equivalents, to SL buprenorphine. This study reported a decrease in pain scores after the initiation of SL buprenorphine therapy for more than two months [14]. Reports of severe withdrawal requiring hospitalization on the day of conversion to buprenorphine have been reported. As we have started converting patients as our standard of care we will collect data on patient important outcomes to document improved outcomes post conversion.

PRELIMINARY RESULTS

We have collected preliminary data on 8 patients that we successfully converted from relatively low dose of chronic opioid therapy to buprenorphine. Table 1 details patient characteristics and outcomes post conversion.

Table 1: Preliminary results from SCD patients who have successfully converted from chronic opioid therapy to buprenorphine.

Pt ID	Hemoglobin Genotype	Sex	Total opioid dose/day prior to conversion (morphine milligram equivalents)	Number of acute pain visits in 6 months prior to conversion	Initial dose of Buprenorphine	Number of acute pain visits in 6 months post conversion	Complications (w/i 72 hours of initiation)
B001	SS	M	34.32 mg	0	Suboxone 2mg/0.5mg	0	NONE
B002	SC	F	137.28 mg	2	Suboxone 24mg	2	Abdominal pain/cramping
B003	SS	M	156.52mg	25	Zubsolv 17.1mg/4.3mg	1	None
B004	SS	M	45 mg	32	Butrans 20mcg	24	None
B005	SS	M	34.32 mg	56	Zubsolv 4.2mg/1.08mg	2	None
B006	SS	F	90 mg	22	Zubsolv 12.6mg	3	Acute pain
B007	SS	M	90 mg	11	Zubsolv 17.4mg	0 (admitted x4 for DKA)	None
B008	SS	M	96 mg	7	Suboxone 8mg	4	None

4. Study Procedures

Prior to enrolling on this trial participants will have already made a decision to convert to buprenorphine therapy after lengthy discussions with the clinical care team. That discussion includes risks and benefits of buprenorphine and the need to be in mild- moderate withdrawal prior to initiating buprenorphine. In addition, most patients will be weaned down as much as possible from their current opioid dose prior to initiating the protocol below.

a. Study design, including the sequence and timing of study procedures.

1. **Within 90 days prior to day 0** subject will sign Informed Consent Form (ICF) (R) , have urine toxicology testing, and complete HRQoL tool (ASCQ-Me) (R),brief pain inventory (BPI) (R), the PROMIS Pain Interference – Short Form instrument (R), and the PROMIS Physical Function – Short Form instrument (R). The ASCQ-Me tool is a validated health related quality tool for use specifically in SCD. The PROMIS Pain Interference instrument measures the degree to which pain hinders social engagement and life enjoyment. The PROMIS Physical Function instrument measures the degree to which pain affects everyday physical activities.
2. Data will be collected on acute care utilization, sickle cell disease co-morbidities from chart abstraction and recorded in case report forms.
3. **Day 0:**
    a. Subject will complete ASCQ-Me, PROMIS Pain Interference, PROMIS Physical Function, and BPI with 7 day anchor (R).
    b. Prior to discharge from SCIC subject will have COWS assessment, pain rating collected.
4. **Day 1:** Subject will return to repeat COWS.
5. Subject will return **day 14**, **day 30**, **day 90**, and **day 180** to repeat ASCQ-Me, PROMIS Pain Interference, PROMIS Physical Function, and BPI (R), or subject will complete these surveys over the phone or online on those days in lieu of coming for a study visit. Acute care utilization will be collected from subject, medical record and Crisp.

a. The only change in the ICF version approved by IRB on November 6 2019 was the option of completing the study surveys remotely (over the phone or online) for participants. Patients that were consented using a previous version of the ICF and are enrolled to the study before the November version, have agreed to all study procedures, but have not agreed to having the option to complete the study surveys online or over the phone. The study team will reach out to these **currently enrolled patients** during in-person clinical visits, via telemedicine appointments or over the phone to re-consent them to the study in-person or remotely using the ICF version approved on November 6 2019. On the instances when the re-consent process is done remotely, the person obtaining the re-consent will:
   i. Sign, print their name, and add date and time of the re-consent, under the consenter line.
   ii. Add on the line of the patient signature: *[First and Last name of patient]* provided verbal affirmation of this newer version of their previously signed consent (the only change from previous signed version by patient is that the surveys can be completed remotely).

6. Data will be extracted from EPIC and CRISP on health care utilization for the 6 months prior to enrollment and 3 years post conversion.
7. We will also collect data on the 15-20 patients that we have now converted to buprenorphine. We will retrospectively review charts to collect genotype data, acute care utilization (ED, sickle infusion clinic and hospitalizations), COWS scores, sex, age and any complications that occurred with conversion. These subjects will be asked to complete ASCQ-Me and Promis tools.

b. (distinguish research procedures from those that are part of routine care).
All research activities are noted with (R) above.

c. Study duration and number of study visits required of research participants.
Each participant will be enrolled for 3 years and will have up to 6 study visits with the possibility of completing the ASCQ-Me, BPI and Promis tools over the phone or online instead of coming in for a study visit. The initial visit is part of routine care that we provide for conversion from opioids to buprenorphine.

d. Blinding, including justification for blinding or not blinding the trial, if applicable. NA

e. Justification of why participants will not receive routine care or will have current therapy stopped.
NA

f. Justification for inclusion of a placebo or non-treatment group. NA

g. Definition of treatment failure or participant removal criteria. NA

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
NA this is an observational trial.

5. Inclusion/Exclusion Criteria

a. Inclusion Criteria:

1. Has SCD, any genotype
2. Is being converted from full agonist opioid therapy to buprenorphine.
3. Able to provide consent
4. Is between the ages 18 and 100.

b. Exclusion Criteria:

1. Unwilling to sign consent.
2. Medical disorder, condition, or history that in the investigator's judgement would impair the patient's ability to participate or complete this study or render the patient to be inappropriate for enrollment.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
NA

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. NA

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. NA

7. Study Statistics

a. Primary outcome variable.
Primary Endpoint: This will be a descriptive study assessing the safety and benefit of converting subjects from full agonist opioids to buprenorphine. Data will be collected on need for hospitalization within 72 hours of conversion due to withdrawal induced VOC, as well as average COWS scores.

b. Secondary outcome variables.
Secondary Endpoint: Measurement of quality of life and decreased pain measured by the BPI, ASCQ-Me, PROMIS Pain Interference, PROMIS Physical Function and decreased acute care utilization.

c. Statistical plan including sample size justification and interim data analysis.
Descriptive study: Paired t-test will be used to compare patient's results on surveys and acute care utilization pre- and post- conversion.

d. Early stopping rules.
NA

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

b. Participants may feel uncomfortable filling out surveys. Steps taken to minimize the risks.
Participants can stop filling out surveys at any time.

c. Plan for reporting unanticipated problems or study deviations.
All study deviations and adverse events will be reported to the IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality. NA

e. Financial risks to the participants.
NA.

9. Benefits

Description of the probable benefits for the participant and for society.
If successful we anticipate that participants will have an improved quality of life with less chronic pain and fewer visits for acute pain management. For society Identifying alternative treatment options for pain management in people with sickle cell disease will help others who are suffering.

10. Payment and Remuneration

Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.
Participants will be compensated $20.00 for each follow-up visit which is not part of usual care. Other costs associated with participation will be part of standard care.

11. Costs

Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.
NA

12. References

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