January 3, 2025

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BRENDAN LEE
BAYLOR COLLEGE OF MEDICINE
MOLECULAR & HUMAN GENETICS

*** * * NOT CURRENTLY APPROVED * * ***

H-45648 - OXYTOCIN TREATMENT FOR HYPERMOBILE EHLERS-DANLOS SYNDROME

APPROVAL VALID FROM 5/8/2024 TO 5/7/2025

Dear Dr. LEE

The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals (BCM IRB) is pleased to inform you that the research protocol and consent form(s) named above were reviewed and approved by Full Board procedures on 5/8/2024 by Board 2.

The study may not continue after the approval period without additional IRB review and approval for continuation. You will receive an email renewal reminder notice prior to study expiration; however, it is your responsibility to assure that this study is not conducted beyond the expiration date.

Please be aware that only IRB-approved informed consent forms may be used when written informed consent is required.

Any changes in study or informed consent procedure must receive review and approval prior to implementation unless the change is necessary for the safety of subjects. In addition, you must inform the IRB of adverse events encountered during the study or of any new and significant information that may impact a research participants' safety or willingness to continue in your study.

Research that has been approved by the BCM IRB may be subject to further appropriate review and approval or disapproval by officials of the institution(s) where the research will be conducted. However, those institutional officials may not approve the research if it has not yet been approved by the IRB.

The BCM IRB is organized, operates, and is registered with the United States Office for Human Research Protections according to the regulations codified in the United States Code of Federal Regulations at 45 CFR 46 and 21 CFR 56. The BCM IRB operates under the BCM Federal Wide Assurance No. 00000286, as well as those of hospitals and institutions affiliated with the College.

Sincerely yours,

JULIE KATKIN, M.D., B.A.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

✓Compare
✓New Compare

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: **H-45648**
Status: Archived
Initial Submit Date: 12/13/2019

Section Aa: Title & PI

A1. Main Title

OXYTOCIN TREATMENT FOR HYPERMOBILE EHLERS-DANLOS SYNDROME

A2. Principal Investigator

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A3a. Financial Conflict of Interest

Does any member of study personnel (Investigator (including investigator's spouse and/or dependent children)) that are involved in the design, conduct, or reporting of the research have a Significant Financial Interest (SFI) that would reasonably appear to be affected by the research for which funding is sought and/or associated with an entity/business that would reasonably appear to be affected by the research?

No

Section Ab: General Information

A4. Co-Investigators

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A5. Funding Source:

Baylor College of Medicine (Internal Funding Only)

A6a. Institution(s) where work will be performed:

BCM: Baylor College of Medicine
Baylor St. Luke's Medical Center (BSLMC)
CNRC: Children's Nutrition Research Center

A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

A8. Therapeutic Intent

Does this trial have therapeutic intent?
Yes

A9. ClinicalTrials.gov Registration

Does this protocol/trial require registration on ClinicalTrials.gov due to it: meeting the definition of an Applicable Clinical Trial, being required under the terms and conditions of an award, or being proposed to be published in ICMJE journals?
Yes

Who will be responsible for registering and maintaining the registration of this Applicable Clinical Trial?
The BCM PI will register the trial because either:

- the trial is BCM PI-initiated,
- BCM is the lead site of this multicenter trial, or,
- the industry sponsor has instructed the BCM PI to register the trial, or,
- registration of this trail is required as a term and condition of the reward by the funding agency.

ClinicalTrials.gov Identifier:
NCT05405257

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

Hypermobile Ehlers Danlos Syndrome is a multisystemic condition involving mainly connective tissues such as joints and skin but may also involve other systems such as the cardiovascular, gastrointestinal, autonomic , and neurological systems. The diagnosis of this condition is based on clinical criteria only and to date, no molecular etiology has been identified. The major component of this condition is generalized joints hypermobility presenting with high Beighton score (acceptably reliable assessment tool for generalized hypermobile joints), joint pain and joint dislocations. Other clinical manifestations may include abnormal scar formation (not as severe as in ' classical type' EDS), cardiac structural abnormalities (mitral valve prolapse and aortic root dilatation), postural orthostatic tachycardia syndrome (POTS), chronic fatigue, atopy, and more. One of the major clinical features that accompany this condition is pain. Pain is usually chronic and can be generalized and/or localized. Pain usually involves the musculoskeletal system with joints and back pain but can involve other systems such as abdominal pain and headache. Neuropathic pain is also a commonly reported in this population of patients. The current approaches to pain management including physical therapy, therapy with pain medications are suboptimal as many individuals continue to have chronic pain with these measures. Thus, new treatment approaches that would help manage pain in this population would be important to affected individuals.

In preliminary studies done in Dr. Lee's lab using primary fibroblasts from patients with hypermobile EDS we revealed changes in oxytocin receptor expression in hypermobile patients when compared with healthy controls. Changes were identifies both at the RNA and the protein levels. Oxytocin (OXT) is a nonapeptide synthesized in the paraventricular (PVN) and the supraoptic nuclei (SON) in the hypothalamus. OXT is an abundant neuropeptide that is mostly known for its importance during parturition and lactation. The use of oxytocin (IM/IV) to induce labor and to prevent postpartum hemorrhage is a standard of care. Multiple published studies suggest a significant role for oxytocin in behavior and pain. OXT function is mediated through postsynaptic receptors. These receptors are widely distributed in several CNS regions, including cortex, olfactory system, basal ganglia, limbic system, thalamus, hypothalamus, brain stem, and dorsal horn of the spinal cord.

The connection between oxytocin and pain was widely investigated both in humans and animal models. Rash, Aguirre-Camacho, and Campbell in 2014 published a systematic review of the literature (1950-2012) to assess the association between oxytocin and pain. They reported that oxytocin increased pain tolerance in 29 of 33 animal studies. The average effect reported by these studies was large (Cohen d=2.28) and effect persisted across central and peripheral modes of administration and type of noxious stimulus used (eg, heat, electric). Analgesic effects were strongest 20 to 30 minutes after exogenous administration and lasted for approximately 1 hour. The results suggest that oxytocin acts as an analgesic for acute pain in animals. Preliminary research with humans offers consistent evidence to suggest that oxytocin decreases pain sensitivity.

The involvements of oxytocin in modulating chronic pain in human was also studied in the past. Effect of oxytocin on chronic pain was evaluated in multiple conditions including irritable bowel disease, chronic constipation, fibromyalgia, and tension-type headache and migraine. Only the study to measure oxytocin effect on irritable bowel syndrome was using IV administration of oxytocin (while all others used intranasal administration). This study showed a significant effect of oxytocin on pain tolerance. Intranasal OXT was reported to relieve headache in a dose-dependent manner in individuals with tension-type headache and migraine.

In this study, we seek to investigate the potential effect of IV oxytocin on chronic pain and its functional consequences in individuals with hypermobile Ehlers Danlos syndrome. Chronic pain will be assessed both by pain scales and by patient-reported outcomes. Functional consequence of chronic musculoskeletal pain will be evaluated using ACTIHEART - a chest-worn device using self-adhesive ECG electrodes that records heart rate, inter-beat-interval (IBI), and physical activity.

Section D: Purpose and Objectives

The purpose of this pilot study is to evaluate effect of IV oxytocin on chronic pain in patients with hypermobile Ehlers Danlos syndrome. The study will evaluate chronic pain before and after treatment with IV oxytocin.

Primary outcome measure 1) Change in the individual's subjective reported pain following treatment with placebo

compared to the change in reported pain following treatment with oxytocin as assessed by the following questionnaires: Numerical pain rating scale, Brief Pain Inventory, and McGill Pain Questionnaire.

Secondary Outcome measures 1) Change in heart rate patterns and activity level following treatment with placebo compared to the change in heart rate patterns and activity level following treatment with oxytocin as an objective functional outcome of pain. 2) Change in reported signs of depression and anxiety following treatment with placebo compared to the change in the reported signs following treatment with oxytocin as assessed by Hospital anxiety and depression scale and State-Trait Anxiety Inventory questionnaires.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

E2. Subjects

Gender:
Female

Age:
Adult (18-64 yrs)

Ethnicity:
All Ethnicities

Primary Language:
English

Groups to be recruited will include:
Patients

Which if any of the following vulnerable populations will be recruited as subjects?

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

All participants in this study are adults and informed consent will be obtained. No vulnerable populations are selected for this study other than women of child bearing potential. The concerns for pregnant women to receive oxytocin will be discussed as part of the consent form signing. A pregnancy test will be obtained prior to the beginning of the treatment.

Anytime consent is obtained, it is incumbent on the individual obtaining the consent to ascertain whether the potential participant understand all aspects of the study. Obtaining informed consent is an interactive process with questions asked of both the investigator and potential participant. A participating investigator or his designee will obtain informed consent and sign the consent form.

All tests will be coded. The database linking coded samples to subject identity will be password-protected, access to which will be limited to essential study staff. Personal identifying information will be recorded in a secure database and consents or other pertinent clinical information stored in a secure file at TCH. Identifiable subject-specific data will not be reported in any public format, nor will it be reported to any third party to which Baylor may contract

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E5. Children

Will children be enrolled in the research?
No

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:

c) Pilot

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This will be a single-site, single-blind, fixed-sequence study to evaluate the effect of IV oxytocin on chronic pain in female adult patients with hypermobile EDS.

Hypermobile EDS is more prevalent in females and the symptoms are usually more severe in females and more females come to medical attention. Oxytocin secretion in the body is dynamic and can be affected by multiple factors including the menstrual period. In order to have minimum variation between tested individuals we chose to conduct this study in females, all participants will be at the same stage of their menstrual cycles. We are not aware of any difference in the risk from using oxytocin in females vs males.

All participating individuals will be individuals affected with hypermobile-EDS (hEDS) with chronic moderate pain. Study will include two periods of treatment - one with placebo and one with oxytocin. Each period of treatment will include three consecutive daily infusions (placebo or oxytocin). Each participant will receive placebo infusion (normal saline) in the first treatment period and oxytocin infusion in the second treatment period. Each period will be preceded by 6 days of daily pain evaluation using pain-evaluation questionnaire ('pre-infusion evaluation'). This period (prior to placebo or prior to oxytocin treatment) will start 1-3 days after the end of the menstrual cycle. Participants will be blinded to the order of treatment.

For each treatment period, participants will arrive to the study site for three daily consecutive visits, each will last for 3-4 hours. Response variables will be collected prior, during and after each infusion. Patients will fill out pain evaluation questionnaires pre and post infusion. Blood pressure and heart rate measurements will be taken prior, during and after the infusion. Blood samples for measurements of oxytocin levels and blood samples for future analysis will be collected prior and after the infusion. Response to treatment by questionnaire will be evaluated also during 6 days after each three infusion days (placebo or oxytocin) . Patients will be asked to wear the ACTIHEART device 3 days prior to infusion, during the 3 days of infusions, and in the 3 days after the last infusion.

Inclusion Criteria:

1) Premenopausal Females, Age >18 years 2) Clinical diagnosis of hypermobile EDS according to the 2017 criteria for hEDS 3) Menstrual periods (range from 8 to 42 days) 4) Pain level greater that pain score of 4 out of 10 on a Numeric Rating Scale in at least two of the following locations: back, neck, shoulders, elbows, wrist, hand joints, hips, knees, ankles, on most days over the 3 months preceding enrollment. 5) On a stable regimen for pain control without any expected increase in dose of pain medications during the study period. 6) All participants should have a negative urine pregnancy test and agree to use an acceptable method of contraception (abstinence or barrier methods). 7) Current from the last year EKG report prior to the infusion for screening purposes. Otherwise, participant will need to have an EKG done in person at the screening visit on site.

Exclusion Criteria:

1) Known allergy to OXT or preservatives in the medication 2) Pregnancy 3) Lactation 4) A confirmed clinical diagnosis of autoimmune disorders that lead to joint inflammation and joint pain such as SLE, RA, psoriatic arthritis, ankylosing spondylitis, scleroderma, and enteropathic arthritis 5) History of known cardiac arrhythmias (except for asymptomatic sinus tachycardia and sinus bradycardia) 6) Heart rate persistently greater than 110/min or less than 50 per minute 7) QTC of > 450 ms from EKG (electrocardiogram) test 8) Taking oral or other hormonal contraceptives 9) Individuals with a clinical condition which, in the view of the investigator compromises safety 10) Participating in another interventional study.

F2. Procedure

This will be a single-blind, fixed-sequence study. This study will include two treatment periods. During the first period, placebo will be administered and during the second period, oxytocin will be administered. The participants will be blinded to the sequence of treatment assignment.

Each treatment period will start 7-12 days after the first day of menstruation and will be divided to the following: 1) pre-infusion period of 6 days during which baseline pain and anxiety evaluation will be done, 2) infusion period that includes 3 consecutive days of infusions, 3) post-infusion evaluation period of 6 days during which post-treatment pain and anxiety will be evaluated.

Pain and anxiety evaluation will be done using the following questionnaires: 1) The Brief Pain Inventory (BPI), 2) Numerical Rating Scale (NRS), 3) McGill Pain Questionnaire, 4) Hospital Anxiety and Depression Scale (HAD), and 5) State-Trait Anxiety Inventory (STAI- trait part) (see section S). Questionnaires will be sent to subjects by secure e-mail, physical mail, or will be handed to the subjects at the beginning of the research period. Subjects will be instructed to complete these questionnaires and return to study staff.

Schedule of Assessments (refer to attachment in section S). This will be provided to study staff only.

Pre-Screen: Eligibility screening of subjects will be done prior to study enrollment. Interested participants will be consented by phone to screen for eligibility purposes.

Eligibility screening will involve: 1) medical record review, 2) collecting history of pain relevant to inclusion, 3) informing patients that pain medication regimens should continue without change during the two weeks prior to the study and throughout the study duration.

Screen Visit: If participants are deemed appropriate candidates for the study, they will come to the study site at BCM/St. Luke's for a screening visit. The screen visit to take place at least one day before the infusion. During the screening visit, the following procedures will be done: 1) signed informed consent, 2) history and physical examination, including vital signs, 3) review of concomitant medications, 4) review of medical records, if available, 5) Urine pregnancy test will be administered, and 6) EKG for assessment of QTc. QTc will be calculated by Fredericia formula. (Current EKG report from the last year prior to the infusion will be used for screening purposes in place of in-person EKG at screen visit.) 7) Enrollment checklist will be completed and 8) receive Actiheart device after study staff goes over instructions for device use. (Actiheart device for monitoring heart rate and movement will be affixed to the chest of the participant with two electrodes. This will be worn for 9 days during the course of the study. if for some reason participants cannot maintain wearing the monitor for 9 days, the study will still proceed.)

Treatment period 1 will start soon after the end of menstrual period for subjects. Treatment period 1 will consist of the following:

A. Pre-infusion Period 1 (will last six days prior to infusion): 1) Questionnaires: Subjects will be asked to complete pain-evaluation questionnaires (BPI, NRS, and McGill). Anxiety evaluation will be completed by patients using HAD and STAI-trait and state parts questionnaires. 2) Participants will be asked to wear the ACTIHEART device during 3 days prior to the infusion, during the 3 infusion days, and in the three days after the infusion. The instructions for the Actiheart monitor and activity record including patient visit reminders will be provided to subjects.

B. Infusion period 1 (Placebo Infusion over three days): Participants will arrive for three consecutive day visits. 1) Subject will be instructed to eat a light, non-fatty breakfast. 2) Vital signs (blood pressure and heart rate), including weight and height will be collected prior to infusion. 3) Provide two questionnaires (BPI, NRS) for subjects to complete. 4) Nursing staff will establish IV access for infusion and blood collection. 5) Prior to infusion, blood samples will be obtained for oxytocin levels and for storage. 6) Placebo infusion (200ml, 0.9% NaCl, over 40 minutes). Blood pressure and heart rate will be monitored during and after the infusion. 7) Blood sample (for oxytocin levels and storage) will be collected immediately after the infusion on day 1. Note: This will require a second vein access to be set prior to the infusion (this sample can not be collected from the place of the OXT / Placebo infusion). 8) Administer both the NPI and STAI-state part questionnaires prior to subject's discharge. Subjects will be discharged 2 hours after the infusion.

C. Post Infusion Period 1 - Pain & Anxiety Evaluation for 6 days: Participants will complete questionnaires over six days at the investigator's discretion: BPI, NRS, McGill on days 1, 3, and 5 after infusion and HAD and STAI-state and trait questionnaires on day 6 after infusion.

Treatment period 2 will start at least 2 weeks after the completion of treatment period 1 and 7-12 days after the first day of menstruation for subjects. Treatment period 2 will consist of the following:

A. Pre-infusion Period 2 (will last six days prior to infusion): 1) Questionnaires: Subjects will be asked to complete pain-evaluation questionnaires (BPI, NRS, and McGill). Anxiety evaluation will be completed by patients using HAD and STAI-trait and state parts questionnaires. 2) Participants will be asked to wear the ACTIHEART device during 3 days prior to the infusion, during the 3 infusion days, and in the three days after the infusion.

B. Infusion period 2 (oxytocin Infusion over three days): Participants will arrive for three consecutive day visits. 1) Subject will be instructed to eat a light, non-fatty breakfast. 2) Vital signs (blood pressure and heart rate), including weight and height will be collected prior to infusion. 3) Provide two questionnaires (BPI, NRS) for subjects to complete. 4) Nursing staff will establish IV access for infusion and blood collection. 5) Prior to infusion, blood samples will be obtained for oxytocin levels and for storage. 6) Oxytocin infusion (200ml, 0.9% NaCl with 1 IU of oxytocin, over 40 minutes*). Blood pressure and heart rate will be monitored during and after the infusion. 7) Blood sample (for oxytocin levels and storage) will be collected immediately after the infusion on day 1. Note: This will require a second vein access to be set prior to the infusion (this sample cannot be collected from the place of the OXT / Placebo infusion). 8) Administer both the NPI and STAI-state part questionnaires prior to subject's discharge. Subjects will be discharged 2 hours after the infusion.

C. Post Infusion Period 2 - Pain & Anxiety Evaluation for 6 days: Participants will complete questionnaires over six days at the investigator's discretion: BPI, NRS, McGill on days 1, 3, and 5 after infusion and HAD and STAI-state and trait questionnaires on day 6 after infusion. Participants will be instructed to mail back the device after completing three days of their last infusion using a prepaid FedEx air bill that will be sent to them by study staff. *Note: The dose oxytocin administration is based on the American College of Obstetricians and Gynecologists' (ACOG) Practice Bulletins for postpartum hemorrhage (see addendum). From the bulletin: Many organizations have recommended active management of the third stage of labor as a method to reduce the incidence of postpartum hemorrhage. Prophylactic oxytocin, by dilute intravenous infusion (bolus dose of 10 units), or intramuscular injection (10 units), remains the most effective medication with the fewest adverse effects". This clinical protocol allows the administration of bolus of oxytocin in a rate of 333 mU/min. We will administer only 1 unit of oxytocin over 40 minutes rate of 25mU/min to avoid any adverse effects.

Texas Children's Hospital REDCap platform may be used for data collection purposes.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 20 Worldwide: 20

Please indicate why you chose the sample size proposed:

There are no published and validated data regarding the distribution of pain scores in individuals with EDS. From our clinical experience and the fact that the inclusion criteria require patients have chronic pain, it would be reasonable to estimate the mean pain levels without any oxytocin treatment to be 7 on the BPI scale. With a sample size of 17 individuals who will undergo treatment with placebo and oxytocin (i.e., matched pairs), we will be able to detect a mean difference in BPI scores of 2 or greater with oxytocin as compared to the placebo with a two sided test with alpha error of 0.05 and power of 0.8. This analysis is based on an estimated effect size index dz of 0.73, an SD in the oxytocin group of 0.66 x mean, the SD in the placebo group being 1.25 x mean, and the correlation between the measures being 0.15. Additionally, we will enroll 3 more participants to account for a drop out rate of 15%. Thus the total sample size would be 20

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

The primary goal of this study is to compare the change in pain scores between the pre and post placebo treatment period vs pre and post IV oxytocin treatment period.

Changes from baseline to endpoint will be evaluated by paired T test

Baseline and endpoint that will be compared:

1) Maximum pain level, minimum pain level, average pain, and pain-effect scores (using the BPI) in the days prior to each infusion period (placebo and oxytocin) and maximum pain level, minimum pain level, average pain and pain-effect scores (using the BPI) in the days prior to each infusion period (placebo and oxytocin) and average pain and pain-effect scores in the days after each infusion period.

2) Comparing the difference in maximum pain level, minimum pain level, average pain and pain-effect scores (using the BPI) pre and post infusion between placebo and oxytocin treatment.

3) Simple pain scale scores (NPRS) prior to infusion and simple pain scale scores 2 hours after the infusion on every day of infusion in both infusion periods (placebo and oxytocin).

4) Anxiety and depression scores prior and post infusion periods and comparing scores following placebo and oxytocin treatments.

5) Changes in heart rate, inter-beat-interval (IBI), and physical activity as measured by ACTIHEART comparing data collected prior, during and after placebo and oxytocin treatments.

In addition we will compare heart rate, blood pressure with oxytocin infusion compared to levels with placebo. We will compare oxytocin levels in the plasma prior to the first infusion, immediately after the first infusion and 2 hours after the first infusion for both placebo and oxytocin.

P-values of 0.05 or less will be considered statistically significant

Section H: Potential Risks/Discomforts

H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

The risks associated with venipuncture are minimal. Adverse events for using IV oxytocin as reported in the literature (based on the use of this drug in pregnant or postpartum women in dose that is at least 10 folds higher than the one used in this study) are as follows:

Common effects - Nausea, Vomiting, loss of appetite, stomach pain Runny nose, sinus pain Memory problems

Rare effects- Anaphylactic reaction Premature ventricular contractions Cardiac arrhythmia Hypertensive episodes

Afibrinogenemia Subarachnoid hemorrhage Intrinsic antidiuretic effect (risk for water intoxication) Postpartum hemorrhage Pelvic hematoma Rupture of uterus (during labor)

In this study we suggest giving a slow infusion of 1 unit of IV oxytocin over 40 minutes. This dose is lower than the dose used in clinical practice and the rate of infusion is slower than the rate that was reported to cause adverse effects in females treated with IV oxytocin to induce labor (Thomas, Koh, and Cooper, 2007 PMID 17142825). Given these data, we estimate that the risk for adverse effects in our study will be very low. Louvel et al (1996, PMID 9014776) published a study that measured the effect of IV oxytocin on threshold of pain caused by colonic distention in males and non-pregnant females with irritable bowel syndrome. In this study subjects were infused with continuous drip of 10, 20, 30 or 50 mU/min oxytocin for 60-70 minutes. In this study four patients receiving oxytocin at a rate of 50mU/min had headache during the infusion and could not continue with the study. No adverse effects had been reported in the other treatment groups that received 10, 20, and 30 mU/min infusion. In our study, the infusion rate will be 1 unit in 40 minutes (25mU/min).

Hypermobile EDS is more prevalent in females and the symptoms are usually more severe in females and more females come to medical attention. Oxytocin secretion in the body is dynamic and can be affected by multiple factors including the menstrual period. In order to have minimum variation between tested individuals we chose to conduct this study in females, all participants will be at the same stage of their menstrual cycles. We are not aware of any difference in the risk from using oxytocin in females vs males.

According to accepted guidelines, the maximum amount of blood to be drawn over a 24-hour period is 3% of total blood volume if the subject is an outpatient, and 5% of total blood volume if the subject is an inpatient. The maximum amount of blood which can be safely drawn from research participants in any one-month period should not exceed 10% of the total blood volume.

All the participants in this study are adults. On average an adult have blood volume of approximately 5 litres. This will allow us to draw maximum of 150 ml per 24 hours and 500 ml over a total period of one month. The amount of blood planned to be drawn will be lower than the maximum allowed. A record of total blood volume withdrawn during each visit will be maintained in the subject's medical record.

Blood drawn during each treatment period (in one month) include: Day 1: Oxytocin levels (10ml) and storage blood (10ml) at preinfusion, immediately post infusion, and 2 hours post infusion. This sums up to 60 ml per 24 hours. Day 3: Storage blood (10ml) at preinfusion and 2 hours post infusion. This sums up to 20 ml per 24 hours. Total of 80ml per one month.

The risk of blood draw may include bruising, pain and infection at the place where the needle was inserted.

For the EKG test, you may develop a mild rash or skin irritation where the electrodes were attached. If any paste or gel was used to attach the electrodes, you may have an allergic reaction to it. This irritation usually goes away once the patches are removed, without needing treatment.

For the ACTIHEART device - mild skin irritation where the electrodes are attached. We recommend that participants will alternate the place of electrodes every day between two suggested sites.

A risk of loss of confidentiality may be possible but every effort by research staff will be made to reduce or eliminate any risk for the subjects.

H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?

Yes

NOTE: The answer to the questions in H2 requires the completion of the form: 'Section H â€“ Data and Safety Monitoring Plan' as an attachment in Section S.

H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?

No or Not Applicable

Is BCM the COORDINATING CENTER for this multi-site research?

No or Not Applicable

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

Chronic, severe, and refractory pain is a significant morbidity in individuals with hypermobile EDS. One potential benefit to be gained by the individual subject participating is the introduction of a treatment that will help in alleviating the chronic pain that individuals with hypermobile EDS experience. Since oxytocin is already an FDA approved drug the possible implementation of this drug in the clinical management of patients with hEDS can potentially be fast.

Describe potential benefit(s) to society of the planned work.

Our study can shed light on the potential role that oxytocin has in alleviating chronic pain in humans in general and specifically in hypermobile EDS. This study will also give information regarding the role of oxytocin in the pathophysiology of hypermobile EDS, a condition that its pathophysiology is unknown.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

Yes. In this study, the dose of oxytocin used is small and we do not expect significant adverse effects of the treatment. Since the pain in hypermobile EDS significantly impairs the individual's quality of life, we believe that revealing new treatments for the chronic pain in this condition outweigh potential risks.

Section J: Consent Procedures

J1. Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?

No

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?

No

J2. Consent Procedures

Who will recruit subjects for this study?

PI

PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

We will contact hypermobile EDS (hEDS) patients that were previously enrolled in another protocol, H-25722. These patients were consented in the past; therefore, we have established a relationship with them allowing us to recontact them. Past and current patients of Dr. Lee may be contacted directly by study staff for possible recruitment.

We will also recruit patients followed by Drs. Jennifer Posey and Shweta Dhar from the adult Genetics hypermobile EDS clinic. These patients may be contacted directly by study staff for possible recruitment/consent. Moreover, subjects referred by other physicians will be approached by study staff after the treating physician receives permission from their patient to do so. Permission to contact these patients can be documented by the referring physician using the Authorization for Study Staff to Contact form attached in section S or via e-mail correspondence from the treating physician. The form or e-mail must be received by study staff before they will contact the potential subject. We will also consider using flyers to recruit clinic patients for this study.

We will recruit patients through the EDS society using the society website and social media platforms. The EDS society will be able to send a notification about this current study using a reference to the study as published in ClinicalTrials.gov or a flyer with details on this study, see attached in section S. Study staff will contact hEDS patients registered in the EDS society's registry who agreed to be contacted by research groups. This will be done through the DICE-EDS program (see https://www.ehlers-danlos.com/eds-global-registry/researcher-applications/).

Consent form will be provided to potential participants in person, via e-mail, by fax, or traditional mail service prior to enrollment so that they have ample time to review the information and ask questions about the study. Investigators or designated research staff will ensure that the participant understands the information provided before obtaining informed consent. Informed consent may be obtained in person or via remote by phone or video teleconference.

When obtaining consent over the telephone or video teleconference, study staff may read or discuss the study parameters of the consent form to the subject which will have been mailed, faxed or sent electronically (e-mail) to the subject in advance of the scheduled phone consent/video teleconference. After subject verbalizes their informed consent for participation and questions have been addressed to their satisfaction, then the designee obtaining consent will document the consent form with their signature and date along with a witness signature/date on the form if applicable regarding the phone consent/video teleconference. Once the subject has signed their consent document, it may be returned to study staff/designee by fax, e-mail (scanned and attached to e-mail) or traditional mail service. When the subject's signed consent is received by the designee, then the designee and witness if applicable will document their signature and date onto the subject's signed consent form. This consent document will then be saved in the study file along with the consent form signed by the designee and the witness that was used to document the consent process. A copy of the consent document signed by all parties may be provided to the subject in person, by fax, via e-mail or by traditional mail service.

Are foreign language consent forms required for this protocol?

No

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?
No

J4. Children

Will children be enrolled in the research?
No

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?
No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?
No

J7. Prisoners

Will Prisoners be enrolled in the research?
No

Section K: Research Related Health Information and Confidentiality

Will research data include identifiable subject information?
Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
Yes

Specific information concerning alcohol abuse:
Yes

Specific information concerning drug abuse:
Yes

Specific information concerning sickle cell anemia:
No

Specific information concerning HIV:
No

Specific information concerning psychiatry notes:
Yes

Demographic information (name, D.O.B., age, gender, race, etc.):
Yes

Full Social Security #:
Yes

Partial Social Security # (Last four digits):
No

Billing or financial records:
Yes

Photographs, videotapes, and/or audiotapes of you:
No

Identifiable biospecimens
Yes

Will identifiable biospecimens be stored for future research?

NA

If yes, is the storage of biospecimens optional for subjects?

NA

Will identifiable private information be stored for future research?

NA

If yes, is the storage of information optional for subjects?

NA

Questionnaire, Survey, and/or subject diary

NA

Other:

No

At what institution will the physical research data be kept?

Each subject will have a hardcopy research file/chart which will be stored in a locked file cabinet at TCH or BCM. These records will not be de-identifed or coded. This is a single-site study, and no case report forms or reporting of patient demographics or personal health information to a central coordinating center will occur. Proof of diagnosis and eligibility, along with paper copies of research-related documents will be kept in these secure files.

How will such physical research data be secured?

Each subject will have a hardcopy research file/chart which will stored in a locked file cabinet at TCH or BCM.

At what institution will the electronic research data be kept?

The electronic research data will be stored and secured through Baylor IT server.

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):

Yes

Such electronic research data will be secured via Other:

No

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?

No

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.

The Actiheart device is supplied by the CNRC team to the research team. The device will be provided to and collected from the participant via FedEx service or will be handed to the patient at one of the research visits (example: screening visit). After the completion of data collection by the participant, the research team will physically hand the device to the CNRC team for further data analysis. Each device will have a patient number that was coded by the research team. CNRC team will have no participant's identifying data on the device. CNRC team will receive subject's gender, height, weight, and date of birth to help in data analysis. For data analysis, CNRC staff has controlled access to the Actiheart device database which is maintained on BCM IT server. Also, the data collected is not shared with device manufacturer or any other third party.

Please note: The CNRC staff has provided the Actiheart device information and will provide statistical analysis for the study.

Where applicable, all research data will be coded and transmitted via secure e-mail accordingly.

Will you obtain a Certificate of Confidentiality (COC) for this study?

No

Please further discuss any potential confidentiality issues related to this study.

N/A

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.

Research-related procedures are incurred by the study. There are no standard of care procedures for this study. Oxytocin will be covered by the study.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:

400

Distribution Plan:

Each completed treatment period will involve $200 in compensation for a total at $400 for study participation. Additionally, reimbursement for applicable travel-related expenses (parking, mileage, ground transport, hotel and flights) will be covered ranging up to but not limited to $600 for study participation. Study compensation and reimbursement will be provided through Baylor's ClinCard program.

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

n/a

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

n/a

Section N: Sample Collection

SAMPLE: Blood

What is the purpose of the sample collection?

Blood will be collected for the measurement of oxytocin levels. Blood will be also collected for storage for later confirmation of research findings.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

All participants are adults. Blood will be collected on day 1 only. The two treatment periods are at least one month apart. On each treatment period, blood will be drawn prior to treatment and immediately after treatment.

Visit 1 in treatment period 1 - blood draw will include in each visit: Day 1 - Pre-treatment: 10 ml (2 teaspoons) for oxytocin measurements, 20 ml (4 teaspoons) for storage. immediately after treatment: 10 ml (2 teaspoons) for oxytocin measurements, 20 ml (4 teaspoons) for storage. Total of 60 ml of blood for this day (12 teaspoons).

Total blood collection during treatment period 1 - 60 ml (12 teaspoons)

Visit 1 in treatment period 2 - blood draw will include in each visit: Day 1 - Pre-treatment: 10 ml (2 teaspoons) for oxytocin measurements, 20 ml (4 teaspoons) for storage. immediately after treatment: 10 ml (2 teaspoons) for oxytocin measurements, 20 ml (4 teaspoons) for storage. Total of 60 ml of blood for this day (12 teaspoons).

Total blood collection during treatment period 1 - 60 ml (12 teaspoons)

Samples for oxytocin measurements will be obtained on ice and plasma will be stored immediately.

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:
Other: Research subject

Will the sample be stripped of identifiers?
No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?
Coded samples may be shared with other researchers. No access to PHI will be shared.

Will sample material be sold or transferred to any third parties? Will the information be de-identified?
No

If sample will be banked for future use:

Where will the sample be banked and for how long?
The blood samples drawn for storage will be processed and stored in locked freezers at the CNRC (Children's Nutrition Research Lab) lab. All frozen samples will be labeled with subject study number only.

Does the banking institution have an approved policy for the distribution of samples?
Yes

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?
Any samples not used during the course of this study will be stored indefinitely and at the discretion of the Principal Investigator.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?
No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?
No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?
If the subject revokes authorization prior to sample processing, all samples including the sample for storage will be destroyed.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?
If the subject revokes authorization, all data gathered from their samples, including storage samples, will be deleted.

Will study data or test results be recorded in the subject's medical records?
No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
Results of cortisol levels can be revealed to the subject as the study is conducted. The results of Oxytocin levels will be revealed to the subject at study completion upon the subject's request. The subject may reveal these results to their doctor.

Please identify all third parties, including the subject's physician, to receive the test results.
No third parties will receive the test results.

SAMPLE: Urine

What is the purpose of the sample collection?
Urine sample will be collected for a urine pregnancy test to determine study eligibility.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.
N/A

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:

Other: Research subject

Will the sample be stripped of identifiers?
No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?
No.

Will sample material be sold or transferred to any third parties? Will the information be de-identified?
No.

If sample will be banked for future use:

Where will the sample be banked and for how long?
No.

Does the banking institution have an approved policy for the distribution of samples?
No.

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?
Yes, any remaining urine sample will be discarded once the urine pregnancy test has been administered.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?
No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?
No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?
Yes, any remaining urine sample will be discarded once the urine pregnancy test has been administered.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?
If data was collected prior to withdrawal, then that data will be kept. Any data collected after withdrawal will be deleted.

Will study data or test results be recorded in the subject's medical records?
Yes

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
Results from urine pregnancy test will be reported in hospital electronic medical record system, i.e., BCM EPIC or BSLMC EPIC.

Please identify all third parties, including the subject's physician, to receive the test results.
No third parties will receive test results.

Section O: Drug Studies

Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance(other than food) that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)
Yes

Does the research involve the use of ANY gene transfer agent for human gene transfer research?
No

O1. Current Drugs

Drug 1: Oxytocin

Is this study placebo-controlled?

Yes

If yes, be sure that you justify the use of the placebo for this research in the space below.

This is a single blind, fixed sequence, placebo-controlled study. Pain levels will be measured under the treatment with placebo in the first treatment period and will be compared to the measurements of the same parameters under the treatment with oxytocin in the second treatment period. This allows the comparison between the same individual subject's response to oxytocin compared to placebo.

Will the research involve a radioactive drug?

No

Section P: Device Studies

Does this research study involve the use of ANY device?

Yes

Device 1: Actiheart

Section Q: Consent Form(s)

Evaluating the effect of IV (intravenous) Oxytocin on chronic pain in adult females with a clinical diagnosis of hypermobile Ehlers-Danlos syndrome (hEDS) that experience chronic pain

Section R: Advertisements

Mode of Advertising: Bulletin Board

Exact language of Advertisement:

ATTENTION: RESEARCH OPPORTUNITY

Baylor College of Medicine is conducting a research study looking at novel treatment option for chronic pain in adult females with hypermobile Ehlers Danlos Syndrome (hEDS)

Purpose of the study is to evaluate the effectiveness of novel treatment option for chronic pain in adult females with hypermobile Ehler Danlos Syndrome (hEDS).

Study involves two treatment periods that each includes a pre-treatment period of six days for chronic pain and anxiety evaluation followed by three days of daily infusions with blood draws along with orthopedic evaluations and ending with a post-treatment evaluation period of six days.

Study location will take place at Baylor College of Medicine McNair Campus and Baylor St. Luke's Medical Center (BSLMC).

Study compensation provided at $200 per completed treatment period for a total of $400 including parking and and other applicable travel-related expenses will be reimbursed.

For more information, please contact: Sayuj Narayan at EDSResearch@bcm.edu

Mode of Advertising: Internet

Exact language of Advertisement:

We will recruit patients through the EDS society using the society website and social media platforms. The EDS society will be able to send a notification about this current study using a reference to the study as published in ClinicalTrials.gov or a flyer with details on this study, see attached in section S. Study staff will contact hEDS patients registered in the EDS society's registry who agreed to be contacted by research groups. This will be done through the DICE-EDS program (see https://www.ehlers-danlos.com/eds-global-registry/researcher-applications/).

Mode of Advertising: Other: BCM Social Media Platforms

Exact language of Advertisement:

We will recruit patients through Baylor College of Medicine social media platforms. Any social media account of Baylor College of Medicine, including but not limited to the Department of Molecular and Human Genetics, will be able to send a notification about this current study using a reference to the study as published on the BCM Clinical Trials Website.

Mode of Advertising: BCM Clinical Trials Website

Exact language of Advertisement:

ATTENTION: RESEARCH OPPORTUNITY

Baylor College of Medicine is conducting a research study looking at novel treatment option for chronic pain in adult females with hypermobile Ehlers Danlos Syndrome (hEDS)

Purpose of the study is to evaluate the effectiveness of novel treatment option for chronic pain in adult females with hypermobile Ehler Danlos Syndrome (hEDS).

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