PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

The purpose of the study is to describe glucose variability in patients with Type 1 Diabetes who have had an islet transplant. Patients who have an Islet Transplantation may have several outcomes including time when insulin is not required followed in some cases by additional insulin for glucose control as patients get further away from transplantation. It is unclear what role automated insulin delivery systems will have in addressing glucose variability in this group of patients who may have some amount of islet function. As a precursor to understanding ways in which automated insulin delivery systems may need to be adapted, we propose to gather data on glucose variability and insulin regimens in individuals who have undergone an islet transplantation.

Objectives/Hypothesis

To describe glucose variability in individuals who have had an islet transplantation.

Study Design: Biomedical

1. Will controls be used? No.

2. What is the study design?

Observational trial in which subjects will receive the same interventions.

Does the study involve a placebo? No.

►**IF YES, provide a justification for the use of a placebo**

Human Participants

Ages: 18 and older
Sex: All
Race: All

Subjects- see below

1. Provide target # of subjects (at all sites) needed to complete protocol. 6

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites. 40%

3. How many subjects will be enrolled at all sites? Up to 40 subjects may be enrolled.

4. How many subjects will sign a consent form under this UVa protocol? Up to 40 subjects

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

1. Type 1 Diabetes
2. Recipient of Islet Transplantation
3. Age 18 and older
4. Females, not currently known to be pregnant. A negative urine/blood pregnancy test will be required for all women of child bearing potential. Subjects who become pregnant will be discontinued from the study.
5. Demonstration of proper mental status and cognition for the study.
6. An understanding of and willingness to follow the protocol and sign the informed consent.
7. Insulin pumps that provides the study team the ability to obtain machine readable formatted data.
8. Access to internet and willing to upload data during the study; use of a personal laptop and ability to access the Internet to provide data to the clinical team so that study equipment can be downloaded.

2. List the criteria for exclusion

1. Pregnancy and intent to become pregnant during trial.
2. Limited use of acetaminophen when CGM is in use
3. Current enrollment in another intervention clinical trial that affects glucose variability.

3. List any restrictions on use of other drugs or treatments.

Limited use of acetaminophen will be allowed. The study physician will have the discretion to discontinue the study subject if continued use of acetaminophen is necessary.

Statistical Considerations

1. Is stratification/randomization involved? No.

2. What are the statistical considerations for the protocol?

As a safety/feasibility investigation, this study is not powered to a specific outcome.

3. Provide a justification for the sample size used in this protocol.

A target sample size of 6 as described above, and we anticipate enrolling up to 40 in order to be sure that we have 6 subjects that have complete the study.

4. What is your plan for primary variable analysis?

We will record CGM metrics with percentage time in range 70-180 mg/dL.

5. What is your plan for secondary variable analysis?

In addition, descriptive glycemic analyses for secondary efficacy measures will be tabulated for each subject based on CGM data, including:

- mean glucose
- percentage of readings in the target range of 70-180
- percentage of readings <70, 60, and 54 mg/dl
- percentage of readings >180, 250, and 300 mg/dl

6. Have you been working with a statistician in designing this protocol? No.

7. Will data from multiple sites be combined during analysis? No

Study Procedures-Biomedical Research

1. What will be done in this protocol?

Visit 1: Screening Visit.

All subjects will be consented and receive a history and physical. Subject exclusion will be at the discretion of the investigator based on study inclusion/exclusion criteria.

At the Screening Visit, the following procedures will be performed / criteria will be checked and documented:

1. Signed and dated informed consent
2. Inclusion and exclusion criteria
3. Demographics (date of birth, gender, race and ethnicity)
4. Medical history
5. Details of the diabetic history such as duration of disease (number of years), diagnosis details, current treatment (including basal rates or basal insulin dose(s), carbohydrate ratios, insulin sensitivity factors, target glucose, average total daily insulin, history of DKA, history of severe hypoglycemia, and self-monitoring blood glucose values)
6. Surgical history
7. Menstrual history (females) and Sexual Activity/Contraception (females)
8. Allergies
9. Medications and supplements
10. Social history including drinking, smoking, and drug habits
11. Physical examination
12. Weight and height
13. Vital signs
14. Pregnancy test - either urine or qualitative serum HCG in women with childbearing potential. If not performed, document reason (surgically sterile, postmenopausal). Result must be negative.

Blood testing will be obtained but will not be reviewed for exclusion criteria. Labs may be obtained at local laboratory (i.e. LabCorp) after consent has been obtained.

- HbA1c assessment via blood draw or fingerstick and DCA2000 or equivalent NGSP-certified point-of-care method (value -4 weeks prior to screening acceptable)
- Comprehensive chemistry panel (within 6 months of screening appointment)
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If a study subject has had a recent physical exam (less than 6 months) and blood work done (within 6 months), the study physician will have the discretion to repeat any test as needed. Once all results of the screening evaluations are available, a decision will be made to determine the subject's eligibility for the study or if one or more parts of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the study subject will be excluded from participation and referred to their primary care physician as needed. If the study subject is pregnant, the study physician will discuss the results of the blood test with the subject, and the subject will be asked to seek confirmation of the test and the appropriate medical care. The total amount of blood to be withdrawn during the screening visit is ~22 cc. The

screening visit will last approximately 2 hours. If the subject cannot schedule Visit 2 within 16 weeks of screening, screening labs, vital signs, and recent medical illness/medications may be re-evaluated. The study physician will have the discretion to repeat any test as needed.

If a subject meets all the study criteria, he/she will be enrolled in the trial. Visit 2 may be completed at the conclusion of Visit 1 if all eligibility requirements are met.

All subjects will also be given instructions to avoid/limit acetaminophen prior to the use of the study CGM or to reschedule their study intervention if they require acetaminophen, as there is potential for interference with glucose oxidase systems for measuring glucose such as the CGM.

Visit 2: Study Equipment Placement & Training and Data Collection Period. Visit 1 and 2 can be done on the same day. All subjects will receive training on the use of the study continuous glucose monitor (CGM) which is a commercially available device (e.g. Dexcom CGM). Subjects will be asked use their personal glucometer and glucose strips for the duration of the trial. Subjects will be asked to bring their personal laptops to this appointment if he/she is agreeable to placing commercially available software on the laptop to facilitate downloading data from the CGM and insulin pump. This software will permit the study team to access the data remotely.

Continuous Glucose Monitor Training

1. An outpatient visit will be scheduled for training on the study CGM.
2. Female subjects of childbearing potential will perform a urine pregnancy test, unless Visit 2 follows immediately after Visit 1. If the test is positive, the subject will discontinue study participation. The subject will be asked to seek confirmation of the test and the appropriate medical care.
3. The subject's insulin pump (if using one), subject's glucometer and study CGM receiver (if using one) will be set using atomic clocks as a reference.
4. The subject will be supervised during the initial CGM sensor placement. A CGM sensor will be inserted into fatty tissue under the skin and will be replaced per manufacturer directions (e.g. 7 days for the Dexcom G5 CGM).
5. If the CGM device experiences a sensor failure while at home, the subject will replace the sensor. The study team will be available for questions or will provide any necessary guidance.
6. The subject will be taught how to calibrate the CGM per manufacturer's guidelines. The subject will be asked to perform all required calibrations with fingerstick glucose measurements.
7. The subject will be taught to look for skin irritation after sensor removal.
8. The subject will be reminded to avoid/limit products per CGM manufacturer guidelines (e.g. avoid acetaminophen 24 hours prior to wearing the Dexcom G5 CGM and while the CGM is in use). Subject who do require acetaminophen will be asked to not to use the CGM values for treatment decisions for 24 hours after taking the medication.
9. If the subject requires an MRI/CT or diathermy, the sensor will be removed from the patient and the reason for removal will be noted. This will not be an adverse event.
10. The outpatient visit will last approximately 1-2 hours depending on prior knowledge of the equipment.
11. The subject will be given an instruction sheet with 24-hour contact information of the research team to address any problems or questions.
12. Unlimited additional appointments and telephone calls to the study team and study physician will be available.

Glucometer Training

1. The subject will be instructed that all fingersticks should be preceded by hand washing with warm water and a dry towel. The subject will be instructed to obtain fingerstick, avoiding alternative sites, when obtaining blood glucose (BG) values. The first drop will be discarded. The second hanging drop will be used to measure the glucose level.
2. The subject will be asked to obtain BG fingerstick required for calibrations. Any additional BG tests normally done by the participant should continue without interruption.

Data Collection Period

1. Subject will collect data for a minimum of 28 days but may continue for up to 3 months.
2. The CGM and insulin administration will be analyzed by the study team. Special emphasis will be noted to the study subject that all meal information (i.e. carbohydrate quantity, insulin and SMBG) must be recorded in their insulin pump if possible.
3. If using Multiple Daily Injections (MDI), subjects will be asked to record injections of insulin using an available commercial application such as Dexcom Mobile App or MySugr app. This app will be placed on the subjects' personal cell phone. A de-identified study email address will be used to establish the account. The study team will access this data and download the data from this account.
4. The subject will be instructed on how to download the equipment. The subject will be asked to provide downloaded data periodically during the data collection period (approximately one time per week) using a web-based diabetes management system (e.g. Diasend, Carelink, etc.) and local diabetes device management software (e.g. Dexcom Studio). The study team will review subject data to ensure proper data collection. Study team will review quantity and quality of the data. Additional download requests may occur depending upon the quality of the data collected.
5. If the subject is unable to provide the downloaded data from home, the subject will be asked to return to the office so the study team can assist them.
6. The subject may return to the office at any time for additional support.
7. A Hemoglobin A1c test may be requested at the conclusion of the Data Collection Period.

2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.

The subject will resume their usual standard of care once study procedures are completed.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
   Study team will assess compliance through evaluation of device downloads/uploads.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
   Study subject who has more than 50% missing data during data collection period. Subject may be asked to repeat data collection period if insufficient data is available.

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