Study Title:

Postprandial glucose control using an extended bolus for high-fat high protein meals in a closed loop system in patients with Type 1 Diabetes

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Postprandial glucose control using an extended bolus for high-fat high protein meals in a closed loop system in patients with Type 1 Diabetes

Study Sponsor
NIDDK

Principal Investigator
Laya Ekhlaspour, MD

Mentors
Dr. Eda Cengiz, MD.
Dr. Bruce Buckingham, MD.

Participating Institutions
UCSF

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PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Postprandial glucose control using an extended bolus for high-fat high protein meals in a closed loop system in patients with Type 1 Diabetes
Précis	A randomized cross over clinical trial using a standard bolus vs. an extended bolus for high fat/high protein (HFHP) meals in adolescents with Type 1 diabetes using a Control IQ closed loop system
Objectives	The objective of the study is to assess the postprandial glucose control following a combination bolus in response to HFHP meals in adolescents with Type 1 diabetes using a closed-loop system which allows for an extended bolus
Study Design	A random order cross over trial: Part 1: Run-in period, Part 2: Meal study using extended versus standard bolus. Following optimization, the participants will be asked to have identical standardized HFHP breakfasts. Insulin bolus infusion for meals will begin prior to meal consumption (time $_{0}$). Participants will be randomly assigned (1:1) in blocks of two to the order in which they receive the two treatments: one group would receive the extended bolus first and one group would receive the standard bolus first.
Number of Clinical Centers	1
Endpoints	Primary Endpoints: Area under the curve between glucose trace and starting glucose (mg/dL*min). Secondary Endpoints: Percentage of time between 70-180 mg/dL; Percentage of time in hypoglycemic range (defined as < 70 mg/dL); Average glucose; Percentage of time in hyperglycemic range (defined as ≥ 180 mg/dL); Insulin dosage; Time to target; Time to baseline; Time to peak glucose; Change in glucose (baseline to max); Peak glucose concentration; and Percentage of time between 70-140 mg/dL
Population	**Inclusion Criteria** 1. Age between 13 and 19 years old, A1C > 6% at screening 2. Diagnosed with type 1 diabetes for at least one year. 3. Total daily dose (TDD) of insulin ≥ 0.3 units/kg/day 4. Currently using the Control IQ closed loop system 5. Willing to abide by meal recommendations and study procedures 6. Willing and able to sign the Informed Consent Form (ICF) and/or has a parent or guardian willing and able to sign the ICF. 7. Use an Android or Apple smart phone 8/ Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 9. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff. 10. Parent/guardian proficient in reading and writing English 11. Live in the United States, with no plans to move outside the United States during the study period **Exclusion Criteria** 1.A1C >10% 2. One or more episodes of severe hypoglycemia or DKA requiring ER visit or hospitalization within the past three months 3. Used non-insulin anti-diabetic medication within the last 30 days other than metformin

	4. Known history of gastroparesis, seizure disorder, adrenal insufficiency, or ongoing renal or hepatic disease 5. Pregnancy or lactation 6. Untreated or unstable hypothyroidism 7. Currently undergoing cancer treatment or systemic treatment with steroids 8. Untreated or inadequately treated mental illness 9. Current alcohol abuse 10. Current illness that would interfere with participation in the study 11. Delayed gastric emptying or any concurrent conditions that can be associated with delayed gastric emptying or altered digestion; and the use of any medication that affects gastric emptying 12. Celiac Disease
Sample Size	Up to 45 screened participants with the goal of randomizing 30 participants.
Participant Duration	4 weeks
Protocol Overview/Synopsis	Once participants are consented and enrolled, they will start a 2-4 week period of optimization with two assessments of their download before entering the second phase of the study. In the second part of the study, the participants will be asked to have identical standardized breakfast that are HFHP. Insulin bolus infusion for meals will begin prior to meal consumption (time 0), and the dose will be adjusted with a correction/reverse correction as needed. Participants will be randomly assigned (1:1) in blocks of two to the order in which they receive the two treatments: extended followed by standard bolus or a standard followed by extended bolus. They may repeat this up to five times.

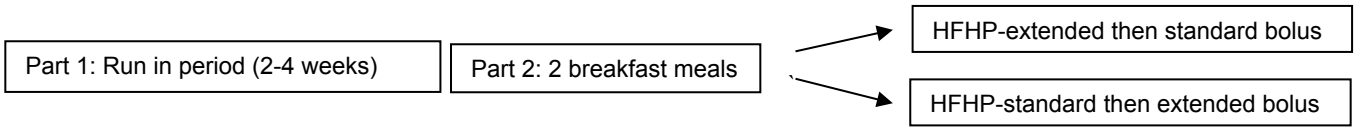

Figure 1: Study Design: A random order cross over trial: Part 1: Run-in period, Part 2: Meal study using extended versus standard bolus. Following optimization, the participants will be asked to have identical standardized HFHP breakfasts. Insulin bolus infusion for meals will begin prior to meal consumption (time $_{0)}$. Participants will be randomly assigned (1:1) in blocks of two to the order in which they receive the two treatments: extended followed by standard bolus

Chapter 1: Background Information

SIGNIFICANCE

The annual incidence of type 1 diabetes in the United States is approximately 22.9 cases per 100 000 people among those younger than 65 years [1]. Severe hypoglycemia, diabetes ketoacidosis, retinopathy, nephropathy, neuropathy, and cardiovascular disease are the major causes of morbidity and mortality in individuals with Type 1 diabetes mellitus (T1D)[2, 3]. Poor glycemic control is associated with an increased risk of both life-threatening acute and chronic complications in patients with T1D [4]. Optimizing glycemic control will decrease the risk of diabetes microvascular complications [5, 6]. Based on American Diabetes Association guidelines postprandial glucose should be less than 180 mg/dl[7]. Unfortunately most of the patients with type 1 diabetes are far from this goal [3, 8] for multiple reasons including: the many, constant tasks that diabetes requires, missed or late meal boluses, miscalculation of meal carbohydrate content [9], mismatches of insulin delivery for a meal because of variable food absorption following a meal due to fat and protein content of the meal [10], fear of hypoglycemia (symptomatic and life-threatening) [11-15], and glycemic changes as a result of exercise [16], illness, menstrual cycles [17], and altered sleep cycles [18]. The goal of this research is to develop closed-loop algorithms that provide adequate insulin coverage for meals having variable fat and protein content while avoiding both hypoglycemia and hyperglycemia.

Optimal postprandial glycemic control is challenging without considering meal composition [10, 19-22]. Continuous glucose monitoring (CGM) has demonstrated that high-fat meals in patients with type 1 diabetes will decrease early gastric emptying and then increase insulin resistance due to increased circulating free fatty acids [23] causing late postprandial hyperglycemia. The impact of dietary fat on glucose homeostasis is via several mechanisms including: modulating GLP1 slows gastric emptying, and increases glucagon (53, 54), GIP promotes lipogenesis (55) and Ghrelin which inhibits glucose stimulation of insulin secretion stimulates glucagon secretion (58, 59). Free fatty acids limit insulin's ability to increase glucose uptake into peripheral tissues and suppresses endogenous glucose production (39). They decrease insulin sensitivity by inhibition of glucose phosphorylation and a reduction in both the rate of muscle glycogen synthesis and glucose oxidation (60, 61).

With high-fat meals, there is, therefore, an increased risk of early hypoglycemia with a premeal bolus because of delayed gastric emptying[24-26]. Even in healthy adults, gastric emptying time was almost doubled following a high-fat meal (67 min vs. 114 minutes)[27]. The early risk of hypoglycemia with fatty meals may be increased with newer faster acting insulins. The fat composition also has distinct effects with high saturated fats causing more insulin resistance[28, 29], and monosaturated fats having a more significant effect on gastric emptying [25]. The mismatch between the delay in insulin effect and the peak meal absorption time reduces insulin's ability to increase glucose disposal and increases the insulin requirement [30].

Currently, carbohydrates are considered the primary and major determinant affecting postprandial glucose control and the insulin bolus is based solely on the carbohydrate content of the meal along with the blood glucose at the time of the bolus[7]. While high carbohydrate meals need large immediate doses of insulin, high fat meals need gradual insulin dosing over a longer time frame following the meal[26]. In a study by Wolpert et.al. [26] a closed-loop system was used to compare high fat (HFD) with low fat dinners (LFD) with identical carbohydrate and protein content. Despite the closed-loop providing additional insulin following high fat meals, there was also more hyperglycemia with the high fat dinner [26].

To determine the amount of insulin to cover carbohydrate, fat and protein meal content it is essential to manage both early and late glycemic responses. In order to determine the incremental differences in postprandial glycemia following a high fat, high protein meal compared with a low fat, low protein meal with identical carbohydrate content and optimize mealtime insulin dosing an open loop model-based approach was recommended by Bell and her group [31]. They recommended that the insulin dose needed to be increased by 65% ±10% and delivered as a combination bolus with a 30% as a standard bolus and 70% given as an extended bolus over 2.4 h to reach the target blood glucose following the addition of 40 g of dietary fat and 27 g of protein to 50 g of carbohydrate. There were also significant inter-individual differences in the effect of dietary fat on insulin requirements and

postprandial BG as well [31]. **Reducing postprandial hyperglycemia remains challenging.**
Studies on the effect of fat content of a meal on postprandial hyperglycemia are not consistent, and little is known about the effectiveness of computed insulin doses for both carbohydrates and fat, on postprandial glucose excursions. Previous findings point to the need for alternative insulin dosing algorithms for higher fat meals. A few studies propose a new insulin delivery profile for better control of postprandial hyperglycemia for high-fat meals [31, 32]. However, the amount and duration of insulin in an extended bolus have not been well studied for a broad range of meals. Most evidence suggests that fat and protein content need to be covered by an extended bolus to achieve better control [32-35]. It is unclear whether the insulin dosing should be obtained via an adjustment to the Insulin Carb Ratio (consistent with fat decreasing insulin's ability to dispose of carbohydrate) or via an additional factor, proportional to the grams of fat (consistent with carbohydrate and fat having independent effects).

It was initially thought that **a closed-loop controller** that assesses **glucose levels** every 5 minutes and has a model of current **insulin** levels would be able to adjust for delayed food absorption through this iterative process every 5 minutes specifically when a premeal bolus was given. One of the major problems with immediate meal coverage [36] is the time delays between increases in glucose levels with the time delays in the onset of insulin action [37]. Once an increase in glucose associated with a meal is detected and insulin is delivered, there is a 20-minute delay before subcutaneously delivered insulin has an effect on glucose levels.

With closed loop systems becoming the standard care and having only one FDA closed loop system with 'extended bolus" option, it is essential to clarify the benefit of the use of extended bolus option following high fat meals.

Use of standardized breakfast to assess postprandial glucose excursion following high fat and high protein meals

In study by King and his colleagues to assess the glycemic impact of different insulin dosing strategies, they used high fat, high protein breakfast in people with type 1 diabetes using multiple daily injections for 4 days. Four different insulin strategies were randomly allocated and tested; 100% of the insulin-to- Carbohydrate ratio (ICR) given in a single dose using aspart insulin, 125% ICR given in a single dose using aspart or regular insulin and 125% ICR given in a split dose using aspart insulin. Postprandial sensor glucose was measured for 5 hr using CGM values [38].

INNOVATION:

Clinical consensus guidelines reinforce the contribution of fat and protein to early hypoglycemia and delayed postprandial hyperglycemia and recommend considering a revised meal insulin dosing pattern with higher fat meals. Currently, the optimal insulin adjustments for high-fat, high-protein (HFHP) meals remain unclear.
This project examines a novel method to consider the effect of meal composition on postprandial hyperglycemia in order to design a new model for insulin dosing in a closed-loop system. This model will be based on assessing the hourly glucose and insulin requirements which could be integrated into prandial dosing algorithms in closed-loop systems in order to optimize postprandial glycemic control. **This study will assess whether setting the percent of insulin required initially and how long the insulin deliver needs to be extended in pumps which allow for extended meal boluses in closed-loop mode.**

The results of this work have the potential to significantly impact one of the most important and challenging parts of diabetes management, postprandial glucose excursions.

Given the known benefits of normalizing postprandial glucose excursions but the variable effect of fat or protein content, in the current application, we propose a study to compare the effect of extended versus standard bolus on postprandial hyperglycemia.
The first generation of closed-loop systems are in fact not fully closed-loop systems and are still quite

burdensome. Multiple companies and institutions are rapidly developing automated insulin delivery (AID) systems. Currently, the time lag from when the glucose begins to rise with subsequent delivery of subcutaneous insulin does not allow current closed-loop systems to adequately manage postprandial glucose excursions and there is both postprandial hypoglycemia and an increased risk of late hyperglycemia. There is only one FDA approved closed-loop system (The Tandem t:slim X2 insulin pump with Control-IQ Technology (Tandem Diabetes Care, San Diego, CA) that has extended bolus as an option. The ability to use an extended bolus as part of an AP system may provide additional flexibility to users to manage their diabetes according to their preferences and lifestyle.

The main features of the Control IQ algorithm include *1*) automated insulin correction boluses administered using CGM data; *2*) a hypoglycemia safety system that uses CGM and insulin-on-board information; and *3*) intensified control overnight [39].

Preliminary Studies:

Extended vs. Standard bolus [40]:

During the initial trials testing the safety and feasibility of a closed loop system, some of the meals were covered by extended bolus. The extended bolus was delivered as 50% of the standard premeal bolus and the remaining 50% delivered over the following 4 hours. Figure 4 compares the glycemic outcome with a standard 100% meal bolus versus an extended meal bolus for a 12-h postprandial period. Median CGM value is plotted for the 12 subjects for 12 h after a high fat dinner with an extended meal bolus (dashed blue line) and without an extended meal bolus (100% bolus upfront) (red line). Five out 12 subjects received the extended bolus for >1 h. For seven subjects the extended portion of the bolus was canceled by the algorithm within 1 hour according to an algorithm safety constraint (when a postprandial glucose value was less than the set point (120 mg/dl) or a negative postprandial rate of change and their data was excluded from analysis [40]. This was a small sample size and there was no statistical significance in glucose parameters with or without the extended bolus. There is clearly a need to repeat these studies with a larger sample size.

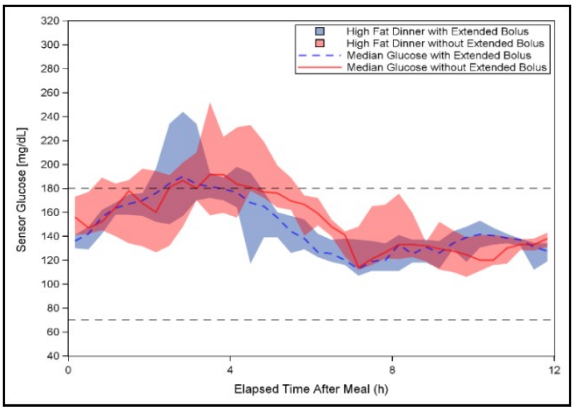

Figure 4: Glycemic outcomes during the 12-h postprandial period after the high-fat dinner with a standard 100%(red) or an extended meal bolus (blue) * CHO = Carbohydrate; BG = Blood Glucose

Closed-Loop Control System

The Tandem Control-IQ closed loop system is a combination of a continuous glucose monitoring (CGM) system, an insulin infusion pump, and software to modulate insulin delivery. The system automatically increases, decreases, and suspends delivery of basal insulin based on insulin delivery history, CGM values, and predicted glucose values. It will also alert the patient when the patient's glucose is heading out of range. Patients still need to bolus insulin for meals/snacks. The Tandem Control-IQ system is one of only two commercially available closed loop systems in the United States, approved by the FDA in December 2019 for commercial use in patients with T1D. Control IQ is the only closed loop system with "extended bolus" as an option.

Figure. t:slim X2 with Control-IQ and Dexcom G6 system

Potential Risks and Benefits

1) Hyperglycemia - High blood sugar and/or ketones could occur with prolonged pump suspension or with an infusion set failure, and high glucose levels can occur with large meals.

2) Hypoglycemia -The frequency of low blood sugar should be no more and possibly less than it would be as part of daily living while the participant is having automated insulin delivery. The insulin will suspend or decrease insulin delivery when there is a risk of hypoglycemia. Because we are asking them to have a high fat meal, there may be a higher rate of early postprandial hypoglycemia with a standard meal bolus.

3) Allergic reaction - Some participants may develop skin irritation or allergic reactions to the tape used to secure the CGM, or to secure the pump. If these reactions occur, different tape will be tried and sites will be rotated frequently.

4) Infection - Whenever the skin is broken there is the possibility of an infection. The sensor and pump infusion sites are inserted under the skin. It is possible that any part of what is inserted under the skin may cause an infection. These occur very infrequently, but if an infection was to occur, oral and/or topical antibiotics can be used.

5) Loss of Privacy - Data downloaded from their pump, glucose sensor and the blood glucose meter will be collected for the study. Some people may be uncomfortable with the researchers having such detailed information about their daily diabetes habits.

Potential Benefits:

The potential benefit of this study gained by participants is a delivery of extended bolus with meals. The results of this work have the potential to significantly impact one of the most important and challenging parts of diabetes management, postprandial glucose excursions.
This type of study will be also immediately beneficial to individuals using an open-loop system that can deliver an extended bolus with meals, and even more importantly, in the future, this data can lead to fully automated insulin delivery without the need for a premeal bolus.

Chapter 2: Study Enrollment and Screening

Participant Recruitment and Enrollment

Enrollment will proceed with the goal of having 35participants randomized.

Informed Consent:

Subjects will be recruited from clinics and through chart review, as well as San Francisco Bay area diabetes support groups. Either by phone, zoom or in person, a member of the study team will explain the purposes, benefits, and risks of the project and offer them an opportunity to ask questions and/or decline participation. The parents of eligible children who are interested in participating will be provided with an informed consent form and HIPAA waiver, either electronically or hard copy. The study team member will then explain the purposes, benefits, and risks of the project and offer them an opportunity to ask questions and/or decline participation. If still interested in participating,

a full description of the nature of the study, the requirements of their participation in it, and the risks and benefits of the study will be explained to potential participants by the principal investigator or a trained research assistant. If an individual declines participation, the reasons for this will be documented and permission to record relevant demographic data from clinic records will be requested. This procedure allows for comparisons to be made between those who do and do not participate. If they consent to participate, they may do so either in written form or electronically, we will have IRB approval for remote consent by Zoom.

Participants Inclusion Criteria:

1. Age between 13 and 19 years old, A1C > 6% at screening
2. Diagnosed with type 1 diabetes for at least one year.
3. Total daily dose (TDD) of insulin ≥ 0.3 units/kg/day
4. Currently using the Control IQ closed loop system
5. Willing to abide by meal recommendations and study procedures
6. Willing and able to sign the Informed Consent Form (ICF) and/or has a parent or guardian willing and able to sign the ICF.
7. Use an Android or Apple smart phone
8. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial
9. Participant and parent(s)/guardian(s) willingness to participate in alltraining sessions as directed by study staff.
10. Parent/guardian proficient in reading and writing English
11. Live in the United States, with no plans to move outside the UnitedStates during the study period

Participants Exclusion Criteria:

1. A1C >10%
2. One or more episodes of severe hypoglycemia or DKA requiring ER visit or hospitalization within the past three months
3. Used non-insulin anti-diabetic medication within the last 30 days other than metformin
4. Known history of gastroparesis, seizure disorder, adrenal insufficiency, or ongoing renal or hepatic disease
5. Pregnancy or lactation
6. Untreated or unstable hypothyroidism
7. Currently undergoing cancer treatment or systemic treatment with steroids
8. Current alcohol abuse
9. Current illness that would interfere with participation in the study
10. Delayed gastric emptying or any concurrent conditions that can be associated with delayed gastric emptying or altered digestion; and the use of any medication that affects gastric emptying
11. Celiac Disease
12. BMI >95th percentile.
13. Individuals with dietary restrictions that prevent test meal consumption

Screening Visit and Eligibility Assessment:

Potential participants will be evaluated for study eligibility through the elicitation of a medical history and local laboratory testing as needed in the judgment of the investigator (as part of usual care).

The screening visit and subsequent scheduled study visits may be conducted virtually via videoconference at the discretion of the study investigator. Screening procedures include a review of inclusion/exclusion criteria to assess eligibility. This information will be verbally elicited from potential participants.

A history will be elicited from the parent and extracted from available medical records with

respect to the participant's diabetes history, current diabetes management, other past and current medical problems, past and current medications, and drug allergies.

At the Screening Visit the following procedures will be performed:

- Informed consent process
- Assessment of eligibility
- Contact information (retained at the clinical center and not entered into study database)
- Demographics (date of birth, sex, race and ethnicity)
- Determination of most recent HbA1c level from medical records or verbal report

Chapter 3.

Run in Period/ Optimization of the insulin management:

There will be up to a four-week run-in phase prior to testing the extended versus bolus. The purpose of this phase is to ensure the subject's insulin settings are as optimized as possible for their personal diabetes management.

The PI/ Clinical staff will review insulin and glucose data and will use clinical judgment to adjust the basal rate, insulin to carbohydrate ratio, and correction factor as needed prior to starting the hybrid closed-loop phase of the study. The data review may be done in person at the study site or remotely according to investigator's preference.

This visit may be conducted in-person at the study site or remotely. For remote visits, the subject's sensor and pump data will be reviewed by the investigator via commercially available data management software. The investigator will instruct the subject/caregiver to make any necessary adjustment to the pump settings. All changes will be discussed with the parent. Changes made to their pump settings will be communicated to their primary endocrinologist at the end of the study.

Randomization:

Visit Timing

The visit, which may be in-clinic or virtual, may occur on the same day as the Screening or Run-in Review Visit, or on a subsequent day. Participants will be randomly assigned (1:1) in blocks of two to the order in which they receive the two treatments: extended followed by standard bolus or a standard followed by extended bolus**.**

Chapter 4: Main Study Procedures

On the day prior to study procedure, participants will attend an in person/virtual visit where they will be provided with a verbal and written description of the study procedure and pre-prepared test meals.

Following an overnight fast (starting at 10 pm), participants will consume the same high fat, high protein test meal for breakfast (6–8 am, within 1 hr of waking), at home, on two mornings within a 2- week period. The insulin dose will be calculated based on the carbohydrate content of the meal and the participant's Insulin to Carb Ratio using the Control IQ bolus calculator. For standard bolus, the 100% of the dose will be given upfront (within 15 minutes before the meal start). For extended bolus 60% of the insulin will be given up front and 40% over 2 hrs.

Participants will be instructed that to avoid exercise on the evening prior to, or morning of the study day. On the morning of the study day, participants will consume the breakfast meal only if their pre-breakfast blood glucose is within the target range (70-180 mg/dl) and no insulin correction insulin dose or hypoglycemia treatment was given after 3 am the same morning.
Prior to meal consumption, participants will be contacted by research team member to confirm adherence to pre-meal requirements; this will be verified using the continuous glucose monitoring and a picture of the meal sent via phone.

Following meal consumption, participants will be allowed to perform only sedentary activities and no further food or drink (except water) will be permitted for 5 hr unless required to treat hypoglycemia (confirmed by glucose meter $\leq$70 mg/dl). At the end of each day, participants will be contacted by the same team member to

review the study day events; again, this information will be verified using the continuous glucose monitoring. **If participants failed to meet study pre-or post-meal requirements, they meal can be repeated up to five times.**

Test meal

KIRKLAND SIGNATURE Nut 2 Bars and 1.5 scoops of whey protein shake mixed with 8 oz of whole milk. The meal contains 51.5 grams carbohydrates, 40.25 grams fat and 54 grams of protein.

Protein Whey shake (ON: GOLD STANDARD)- extreme milk chocolate
1 scoop (32 grams)
Fat 1.5 gram
Carb 3 gram
Protein 24 grams
Calories 120

Whole milk (8 ounces)
Carbs 13 grams
Protein 8 grams
Fat 8 grams
Calories 150 c

KIRKLAND SIGNATURE Nut bar
1 bar (40 grams)
Fat 15 grams
Carbohydrates 17 grams
Protein 5 grams
Calories 200

Data Review:
Glucose data will be reviewed using Dexcom CLARITY® software (Dexcom Inc., San Diego, CA, USA).

Insulin data will be downloaded using tidepool or the t:connect® Diabetes Management Application (Tandem Diabetes Care, San Diego, CA). If the data is not available on tidepool, Tandem Diabetes Care will provide the data using the pump serial numbers and the study dates.

Statistical analyses

Primary Endpoint: Area under the curve between glucose trace and starting glucose (mg/dL*min)

Secondary Endpoints: Percentage of time between 70-180 mg/dL; Percentage of time in hypoglycemic range (defined as < 70 mg/dL); Average glucose; Percentage of time in hyperglycemic range (defined as ≥ 180 mg/dL); Insulin dosage; Time to target; Time to baseline; Time to peak glucose; Change in glucose (baseline to max); Peak glucose concentration; Percentage of time above 250 mg/dL; and Percentage of time between 70-140 mg/dL.

Analytic Approach: Normality of the differences between standard and extended bolus strategies was tested using Shapiro-Wilk and Kolmogorov-Smirnov tests. The endpoints were then analyzed using a paired t-test and Wilcoxon signed-rank test with Hodges-Lehmann estimate of the median difference and corresponding 95% confidence interval. Time to targe and Time to baseline were additionally analyzed with a penalized cox proportional hazard model. The same methods were also used to calculate and compare the amount basal insulin, bolus insulin, and total insulin delivered over two, three, and five hours.

Additional statistical analyses may be conducted as necessary to support the objectives of the study and to appropriately interpret the data.

Sample size and power calculation: Based on our preliminary analysis of the high fat vs. low-fat meal data, assuming a standard deviation of [AUC]G>140 of 3000 mg/dL.min, a sample size of 30 subjects provides 80% power to detect a clinically meaningful difference of 1600 mg/dL.min in AUCs for standard vs extended bolus with a type I error rate of 0.05.

Risk Assessment:

Research involves greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. The research presents more than minimal risk to children, but holds out the prospect of direct benefit for the individual subject or is likely to contribute to the subject's well-being. The extended bolus is expected to reduce hypoglycemia without incurring an unacceptable increase in hyperglycemia and the extent and magnitude of hyperglycemia associated with meals.

Protection against the risks:

There will be a run-in phase prior to testing the extended versus bolus. The purpose of this phase is to ensure the subject's insulin settings are as optimized as possible for their personal diabetes management. The PI will be reviewing each subject's data during this run-in phase and suggest changes.

We have a Data Safety Monitoring Board as an independent group of experts to evaluate the data and make recommendations concerning the continuation, modification, or termination of the trial. The PI and her mentor will review the data following the completion of phase 2 (testing standard versus extended bolus) for each participant as well. If following the completion of the study for 10 subjects, more than 20 percent of the participants experience hypoglycemia (less than 50 mg/dL) attributable to study intervention, the study will be suspended. An assessment of the risks to patients will be made and a recommendation to discontinue the study will be made to the IRB.

All members of the research team have and will maintain current training in the ethical conduct of research. Dr. Ekhlaspour has completed rigorous training in the protection of human subjects. Research assistants and mentors/advisors working on the project will also complete standardized training in the protection of human subjects. The plan for protecting privacy and confidentiality recognizes that the protection of privacy in studies involving sensitive data is of utmost importance. All clinically-relevant and study information will be kept in locked files in locked offices or password protected files.

Participant identity will be kept as confidential as possible as required by law. Personal health information related to this study may be disclosed as authorized by the participant. Research records may be disclosed

outside of the UCSF, but in this case, they will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, participant identity will not be disclosed.

All participants may contact the Protocol Director and a study staff with any concerns or in the event of adverse event.

We have a Data Safety Monitoring Board as an independent group of experts to evaluate the data and make recommendations concerning the continuation, modification, or termination of the trial. Any seizure, loss of consciousness or episode of DKA will be reported to the IRB and DSMB. The PI and her mentor will review the data following the completion of phase 2 (testing standard versus extended bolus) for each participant as well. If following the completion of the study for 10 subjects, more than 20 percent of the participants experience hypoglycemia (less than 50 mg/dL) attributable to study intervention, the study will be suspended. The treatment of hypoglycemia will be according to the standard of care. An assessment of the risks to patients will be made and a recommendation to discontinue the study will be made to the IRB.

Grading of Adverse Events:

For purposes of monitoring and reporting adverse events, the following NIH definitions will be used: Adverse Event (AE): any unanticipated, untoward medical occurrence that may present itself during treatment or administration of an intervention, and which may or may not have a causal relationship with the treatment. Adverse events could arise from the study (e.g., breach of confidentiality) or could arise due to the population under study. Serious Adverse Event (SAE): Any medical occurrence that results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalizations; creates persistent or significant disability/incapacity, or a congenital anomaly/birth defect

Documentation and Reporting of Adverse Events

All AEs that occur after the subject has been enrolled in the trial will be documented in the CRF and will include date of onset, date of resolution, name or brief description of the event, treatment given for the event, severity, relationship to study intervention, action taken, outcome, and whether the event was classified as serious. A physician will determine the relationship of the event to the study. Anticipated events relative to the population under study will be noted as potential risks on the informed consent form. The DSMB will also monitor the occurrence of these events. Should any other problems or concerns arise with the data collection or intervention program, the PI or co-Is will be available to address these.

SAE's that are at least possibly related to therapy received as part of participation in this trial, unexpected, and severe will be reported within 3 days to the IRB. A listing of all other adverse events will be sent to the IRB biannaully.

Subject Compensation:

Participants will be compensated $150 for their participation in the study.

Participation in the study is voluntary, and a subject may withdraw at any time. The investigator may withdraw a subject who is not complying with the protocol. For subjects who withdraw, their data will be used up until the time of withdrawal.

Subject Discontinuation Criteria

Subjects who become pregnant will be discontinued from the study. The investigator may withdraw a subject who is not complying with the protocol. Withdrawal of a subject will be considered for the following reasons: 1) Failure to monitor their sensor; 2) Infusion set failure 3) developing >1.0 mmol/L ketones

For subjects who withdraw or who are withdrawn, their data will be used for analysis purposes up until the time of withdrawal.

References

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