Hypoglycemia Protocol,
Version 1.3 22 July 2015
Version 1.2 06 May 2015
Version 1.1 27 June 2014
Version 1.0 October 30, 2013

Study: Impact of hypoglycemia on cardiac function in elderly patients with diabetes

Purpose:
To determine how frequently hypoglycemia occurs in older patients with diabetes, and determine if hypoglycemia adversely affects cardiac function in these patients.

Hypothesis:
Hypoglycemia can result in abnormalities in cardiac rhythm and autonomic function and can cause myocardial ischemia in elderly patients with diabetes.

Objectives:
1. To monitor blood sugar and cardiac function continuously for 6 days.
2. To determine if there is a correlation between hypoglycemia and alterations in cardiac rhythm, alterations in cardiovascular autonomic function and myocardial ischemia.
3. To collect baseline data to design a subsequent study to assess the effects of various interventions designed to protect the cardiovascular system against hypoglycemia if objectives 1 and 2 are achieved.

Background:
A variety of studies have shown that the risk of severe or fatal hypoglycemia associated with the use of insulin or oral agents increases exponentially with age (Meneilly). Hypoglycemia due to these agents is the commonest reason for iatrogenic hospitalization in the elderly (Budnitz). There are several reasons for this increased prevalence (Meneilly). The most important counter-regulatory hormone in the defense against hypoglycemia in normal subjects is glucagon, and the responses of this hormone to hypoglycemia are impaired in normal elderly subjects and, to an even greater extent, in elderly patients with diabetes. Many elderly patients have not been educated about the warning signs of hypoglycemia and, as a consequence, do not know how to interpret these symptoms when they occur. In addition, even when they are educated about them, elderly patients have reduced awareness of the autonomic warning symptoms of hypoglycemia (such as sweating, shakiness and a feeling of hunger). Finally, older patients have impaired psychomotor performance when their blood sugars are low, which prevents them from taking the appropriate steps to return their blood sugars to normal. Thus, the increased severity of hypoglycemia in the elderly is due to a variety of abnormalities, including decreased counter-regulatory hormone secretion, reduced knowledge and

awareness of warning symptoms, and altered psychomotor performance. Indeed, recent data suggest that asymptomatic hypoglycemia is shockingly common in these patients. When assessed by continuous glucose monitoring, 65% of elderly diabetic patients have frequent hypoglycemic episodes lasting up to an hour that are entirely asymptomatic (Munshi, Meneilly). The consequences of frequent, severe and/or asymptomatic hypoglycemia in this patient population have not been clearly defined. The risk of hospitalization and death is detailed above, but this is probably a "tip of the iceberg" phenomenon since hypoglycemia is so frequently asymptomatic in this age group. It is known that severe hypoglycemia increases the risk of dementia (Meneilly). Older patients on insulin have an increased frequency of falls and fractures, and this is more likely as the HgbA1C falls, implying that low blood sugars may be a contributing factor (Meneilly). Elderly patients with diabetes have an increased frequency of syncope, cardiac arrhythmias, myocardial infarction, and sudden death and the risk of these events is more than doubled in patients treated with agents that are known to cause hypoglycemia (Currie). However, other than some anecdotal reports of low blood sugars at the time of these events, no studies have carefully evaluated the relationship between hypoglycemia and cardiac function in this age group. In this study we propose to evaluate the association between hypoglycemia, as measured by continuous glucose monitoring, and cardiac rhythm, cardiovascular autonomic function and myocardial ischemia, as measured by continuous electrocardiographic (ECG) monitoring.

Design, Specification of Endpoints, and Procedures:

We propose a pilot study in 20 patients over age 70 *who have had type 2 diabetes for at least 5 years and are being treated with insulin ~~glargine~~. All patients will have a BMI of between 20 and 35 Kg/M2, and an A1C between 7 and 8.5 %. All patients will have well controlled hypertension and hyperlipidemia. Patients with a GFR less than 40ml/min, poorly controlled CHF and active coronary artery disease or cerebrovascular disease will be excluded, although a past history of CAD or stroke will not result in exclusion. We will also exclude patients who are not fluent in English.* These patients will be enrolled from the elderly diabetes clinic at Vancouver General Hospital. Patients will be contacted as per the information in the letter of initial contact. Briefly, appropriate patients will be sent a letter describing the study. At least one week later they will be contacted by a research nurse/research assistant who will explain the study, answer their questions, and if they agree to participate, will send them a copy of the consent for their perusal. If, after reading the consent, they are still interested in participating, they will be asked to come to the VGH Diabetes Centre of Gerontology Research Laboratory in the Research Pavilion at Vancouver General Hospital. At that time, a trained research nurse will instrument each patient with an iPro2 glucose sensor (Medtronic Canada). These sensors reliably and continuously measure blood glucose for periods of up to 7 days. Briefly, the skin will be swabbed with a disinfectant and a small catheter will be inserted subcutaneously. This catheter will be attached to a glucose sensor. Patients will

wear this sensor for 6 days. They will measure their glucose using a glucometer 4 times each day during this period and will also be given a log book to keep track of glucose values. They will also be asked to record any symptoms of hypoglycemia. At the end of 6 days the sensor will be removed.

At the same time the glucose sensor is started, a trained research nurse will connect the patient to an Icentia CardioSTAT, a continuous ambulatory ECG cardiac monitor. The Icentia CardioSTAT is a new heart monitor designed to record up to 7 days of continuous single-lead ECG in ambulatory conditions. The device has the shape of a thin, flexible strip of about 14cm x 3 cm to be applied on the subject's upper torso at the level of the second intercostals space. The CardioSTAT is held in place by means of 2 standard ECG gel electrodes (3M™ Red Dot™ 2560) allowing the skin to breathe freely underneath its' surface. A Hypafix dressing will be placed over the electrodes.The CardioSTAT is single-use. A new unit will be used for each subject.

Subjects will be asked to contact the study site if they are experiencing any discomfort, redness or irritation under the electrodes/Hypafix dressing. If needed, a clinic visit will be scheduled to assess and/or replace the electrodes/Hypafix dressing. At the end of the recording period the Cardio STAT will be returned to the manufacture for data download and proper disposal.

The CardioSTAT will not be used if the subject has 1) a chronic skin disorder on the upper torso; 2) an open wound, cut abrasion, burn or flaking skin at the application site; 3) known allergies to medical tape; or 4) presence of an active implantable device (such as a pacemaker, defibrillator, neurostimulator).

The archived ECG waveforms will be downloaded for QT and TWA analysis. The heart rate and QT interval will be measured at baseline and the end of each interval from the digitized ECG.

Patients and relevant family will be provided with in person and paper based education regarding the function and use of the monitor, implications for bathing and sleep, and contact information for troubleshooting. They will be asked to keep a log book of any cardiac symptoms during the 6 days of the study, as well as their activities. The iPro2 glucose and CardioSTAT monitors will undergo time synchronization to ensure ability to do correlative analysis.

This is a feasibility pilot to establish preliminary data for analysis. The CardioSTAT monitor will allow assessment of cardiac arrhythmias, myocardial ischemia and cardiovascular autonomic function. The results from the glucose sensor and the CardioSTAT monitor will be correlated and compared to each other to determine if hypoglycemia has an adverse effect on heart function. Hypoglycemia is likely to induce autonomic responses captured on the CardioSTAT and concordant ischemic ST changes if coronary disease is present. It may also detect any resultant arrhythmias, although ischemic arrhythmias are

uncommon in 6 days of monitoring. If we determine that hypoglycemia has negative effects on cardiac function, we may able to design treatments that would prevent these effects from happening in the future.

Data Analysis:
Autonomic function will be evaluated by assessing heart rate variability using autoregressive spectral analysis during hyperglycemia, euglycemia and hypoglycemia. Arrhythmia analysis will be performed using the standard algorithms that are normally used to assess data in the Holter laboratory, and will be correlated with prevailing blood sugar values. This will include standard diagnostic evaluation including mean, median and range of heart rate, quantitation of supraventricular and ventricular ectopy, and Tpeak-Tend. P wave duration and variability and T wave alternans will be measured as well and correlated with prevailing glucose values. ST segments to evaluate for ischemia will follow standard techniques in routine clinical software (GE Marquette, Wisconsin) that reports ST shifts during 5 minute epochs, and will be correlated with metrics of heart rate variability, absolute heart rate and symptoms.

Measurements will be performed by an experienced expert blinded to the patient's clinical status. QTc will be calculated using Bazett's formula (Bazett). The end of the T wave will be defined as the intersection of the maximum slope of the terminal T wave with the isoelectric TP segment. QT variability will be evaluated from digitized lead V_2 at baseline. Each 5-minute epoch will be analyzed using a validated QT interval measurement algorithm proposed by Berger et al. (Berger), which computed mean QT, QT variance, mean heart rate, and heart rate variance. To measure beat-to-beat QT variability, a normalized QT variability index (QTVI) will be calculated. TWA will be measured from the digitized ECG using the spectral method as previously developed by the University Health Network Holter data site (Selvaraj). TWA magnitude (V_{alt}) will be quantified over a 128-beat window which will be successively incremented by 16-beats until the end of each 5-minute epoch.

Statistical Analysis:
Continuous variables will be expressed as mean and standard deviation or median and interquartile range (25^{th}-75^{th} percentiles) where appropriate. *Student's paired t test or the Wilcoxon signed rank test* and One-way repeated measures ANOVA or the Friedman test will be used for comparison as appropriate. The within-subject variance-covariance matrix will be evaluated by the compound symmetry method. Categorical variables will be presented as frequency or percentage. Fisher's exact test will be used for comparison at each glucose level. Cochran's Q test will be used for comparison of proportions. A two-tailed p-value <0.05 will be considered statistically significant. Statistical analysis will be performed using SPSS (version 15.0.0, SPSS Inc.) and SAS version 8.2 (SAS Institute, Cary, NC).

Potential benefits:
Information gained from this study will expand the knowledge base with respect to the impact of hypoglycemia on cardiac function. If we find that individual patients experience low blood sugars, we will alter their therapy to see if this can reduce the frequency of these events. If the CardioSTAT monitor shows that patients have any abnormalities in cardiac function, we will suggest a plan of investigation and management to their family doctor. This could involve recommendations regarding unrecognized atrial fibrillation with attendant stroke risk (by definition $CHADS_2$ score ≥2), or ventricular arrhythmias.

Risks:
There will be some discomfort associated with the insertion of the glucose sensor. There is a small risk of skin infection from the insertion of the glucose sensor and the possibility of an allergic reaction from the tape used to apply it and the CardioSTAT Monitor leads. This risk occurs less than 1 in 1000 times the sensor is used.

Investigators:
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