PROTOCOL TITLE: Use of NPH versus Basal Bolus Insulin for Steroid Induced Hyperglycemia

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Study Site:

Northwestern Memorial Hospital

Study identifiers:

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OBJECTIVES:

1.) To determine which insulin regimen, NPH in addition to basal/bolus insulin or just basal/bolus insulin, provides better glycemic control in patients on once daily dosing of steroids
2.) Determine which dosing regimen leads to less adverse events, specifically hypoglycemia

BACKGROUND:

Glucocorticoids are known to cause an increase in insulin resistance, leading to hyperglycemia, in both diabetic and non-diabetic patients. In both the inpatient and outpatient setting, steroids are used for their anti-inflammatory property to treat a variety of conditions. There is a paucity of information regarding the best way to treat steroid-induced hyperglycemia. Generally insulin is administered in the hospital using a basal/bolus approach, i.e. giving a long-acting insulin such as glargine to control hepatic glucose production overnight and between meals and giving a short-acting insulin as a bolus before meals to control the postprandial rise in glucose. Approaches that have been used to adjust for the additional hyperglycemia induced by high dose steroids, which are usually administered once daily in the morning, include the addition or substitution of NPH insulin for glargine insulin vs. adjusting the basal/bolus regimen.

In 2008, Bevier et al investigated increasing doses of total daily insulin needed in Type I diabetic patients on an insulin pump who were administered a fixed dose of steroids for three days. The study noted an increase in basal rates and insulin boluses required after six hours following the first dose of prednisone due to rising insulin resistance. The study concluded that insulin doses should be increased by at least 30% when the corticosteroid therapy is started but may need to be increased by up to 70% or more to normalize blood glucose levels[4]. While it is known that steroids cause an increase in insulin resistance and an increased total daily dose of insulin requirements; the best way to administer this insulin is still unknown.

While some studies have looked at using NPH versus glargine as basal insulin for steroid-induced hyperglycemia[1,2,3], few studies have looked at the addition of NPH to a basal bolus regimen for treating steroid-induced hyperglycemia.

A pilot study done at the University of Colorado looked into the use of NPH plus basal bolus insulin versus just basal bolus insulin doses to treat steroid induced hyperglycemia, specifically in cystic fibrosis related diabetes patients receiving methylprednisolone.[5] Similar to Beiver et al[4], they concluded that with the addition of steroids, there was an overall increase of total daily doses of insulin by 40%; half of the arm received this increase in the form of NPH in addition to glargine and lispro while half of them received this in the form of an increase in the glargine and lispro doses. The study showed that methylprednisolone raised prelunch and predinner glucose levels in patients treated with glargine/lispro alone; however, the addition of NPH with methylprednisolone significantly decreased the rise in postprandial glucose at lunch and dinner compared to the glargine/lispro group but still did not return the glucose levels to acceptable levels.[5]

Our study aims to further study the use of NPH in addition to glargine and lispro in the setting of steroid use to achieve improved glycemic control in the inpatient setting.

References:

1. Dhital SM, SHenker Y, Meredith M, Davis DB. A retrospective study comparing neutral protamine Hagedorn insulin with glargine as basal therapy in prednisone-associated diabetes mellitus in hospitalized patients. Endocrine Pract 2012;18: 712–719.

2. Ruiz de Adana MS, Colomo N, Maldonado-Araque C,et al. Randomized clinical trial of the efficacy and safety of insulin glargine vs. NPH insulin as basal insulin for the treatment of glucocorticoid induced hyperglycemia using continuous glucose monitoring in hospitalized patients with type 2 diabetes and respiratory disease. Diabetes Res Clin Pract. 2015;110:158–165.

3. Radhakutty A, Stranks JL, Mangelsdorf BL, et al. Treatment of prednisolone-induced hyperglycaemia in hospitalized patients: Insights from a randomized, controlled study. Diabetes, Obes Metab 2017;19:571-578.

4. Bevier WC, Zisser HC, Jovanovic L et al. Use of continuous glucose monitoring to estimate insulin requirements in patients with type 1 diabetes mellitus during a short course of prednisone. J Diab Sci Technol 2008;2: 578–583.

5. Seggelke SA, Gibbs J, Draznin B. Pilot study of using neutral protamine Hagedorn insulin to counteract the effect of methylprednisolone in hospitalized patients with diabetes. J. Hosp. Med., 2017;6:175–176.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria:

- Patient's receiving once daily dosing of methylprednisolone in a dose of 10 mg/day or greater or prednisone in a dose of 12 mg/day or greater
- Hyperglycemic (Glucose > 126 mg/dL) diabetic and non-diabetic patients
- Age Range: > age 18
- Expected duration of hospital stay and time on steroids $\geq$ 3 days
- Patient or appropriate caregiver able to give Informed Consent

Exclusion Criteria:

- Patient's with two or more doses of methylprednisolone/prednisone per day or other steroids, such as hydrocortisone or dexamethasone
- Pregnancy
- eGFR < 45 ml/min/1.73m^2

STUDY TIMELINES:

Once a participant is recruited for the study, participants will be followed for three days with the intervention on the inpatient service. Anticipated duration of enrollment will be 2 years.

STUDY ENDPOINTS:

Primary endpoint: Determine which of these regimens is superior with respect to glycemic control in these two groups.

Secondary Endpoints: A secondary outcome will be to determine which of these regimens will result in less hypoglycemia.

PROCEDURES INVOLVED:

Subjects

Our study aims to recruit 25 inpatients at Northwestern Memorial Hospital to each study arm. Eligible patients will be those who are receiving once daily dosing of prednisone or methylprednisolone for any medical condition. Examples include patients being treated with steroids for respiratory issues, stem cell transplant patients, and cystic fibrosis related diabetes patients. This will be a prospective, randomized control study in which each patient will be randomized to one of two arms. Consent will be obtained at the initial day of an Endocrine or Glucose Management Service (GMS) inpatient consult, and then subsequently randomized.

Study Intervention

One group will receive NPH in addition to their current glargine lispro basal/bolus regimen at the time of the prednisone administration. Another group will continue to receive glargine and lispro; however, their basal and bolus regimens will be increased (see attached tables for details).

DATA AND SPECIMEN BANKING:

Data will be stored both in a locked cabinet and password protected computer and deidentified data will be stored on endocrine FSM research server (R Drive) where only study personnel will have access.
Only the investigators in the study will have access to the data.
Data will be stored until final analyses and all publications have been completed and will then be destroyed by erasing any stored files on the computer and any printed out data.

There will be no specimen banking.

DATA AND SPECIMEN MANAGEMENT:

An analysis of the routine finger stick capillary blood glucose levels will be done (see below). No extra fingersticks will be carried out just for the study. Glycemic control will be assessed by measuring the mean of the 4 glucose levels (premeal and bedtime) for the first 3 days of treatment and comparing these means between the groups. A secondary analysis will be to compare the proportions of values in

the therapeutic targets of 80 – 140 mg/dL and 80 – 180 mg/dL. An additional analysis will compare the proportion of values < 70 mg/dL, the threshold value for hypoglycemia.

In the study by Seggelke et al (5), the 3 day means of 3 daily premeal glucose levels for the two groups (basal/bolus alone vs. basal/bolus + NPH) were 241 and 176 mg/dL (a difference of 65 mg/dL) with standard deviations of 36 and 28 mg/dL for the two groups. If we assume that our modified basal/bolus regimen gives improved glycemic results comparable to theirs, we have assumed the following for our statistical power calculations: a standard deviation of 30 mg/dL and assume half the difference in the means of about 30 mg/dL, which can be considered to be clinically significant, then a sample size of 20 in each group would have statistical (two-tailed) power of 0.869 to demonstrate this difference between the groups of 30 mg/dL using an alpha=0.05. We plan to recruit 25 in each group to allow for drop-outs, because some patients may not stay on methylprednisolone/prednisone for 3 days.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:

There is always a risk of both hyperglycemia and hypoglycemia when managing hyperglycemic patients with insulin and it is not known which of our two approaches will be better with respect to reducing hyperglycemia and hypoglycemia. Each patient will have a routine consultation by the Endocrinology Consult Service (ECS) or the Glucose Management Service (GMS) and will have blood glucose levels monitored at least daily by those services. If glucose levels are outside the target range of 80 – 180 mg/dL, insulin doses will be adjusted accordingly by those services. Cumulative data, including the frequency of hypoglycemia, will be reviewed by the Principal, Co-Principal and Fellow Investigators after the first 3 patients are entered into each group and then after every 5 patients in each group to determine if the basic algorithms (see Table) need to be adjusted.

WITHDRAWAL OF PARTICIPANTS:

Participants with be withdrawn from the study if their steroid regimen changes or stops from once a day dosing of methylprednisolone or prednisone.

RISKS TO PARTICIPANTS:

Risks: A confidentiality breach is a risk associated with data review research. As noted above, both hyperglycemia and hypoglycemia are inherent risks with inpatient glycemic management with insulin. Every effort will be made to reduce these by at least daily review of blood glucose levels on every participant with adjustments of insulin doses as needed.

There are no dangers to an embryo/fetus from insulin but we plan to exclude women known to be pregnant. Because there are no known dangers from insulin, we do not plan to do pregnancy tests, however.

POTENTIAL BENEFITS TO PARTICIPANTS:

Benefits: The participants are not likely to receive any benefit from the proposed research; however, society and investigators will benefit from the knowledge gained. As with all patients seen by the ECS and the GMS, patients will benefit from having their glucose levels monitored closely with frequent insulin adjustments made as needed.

VULNERABLE POPULATIONS:

No vulnerable populations will be included in this study

COMMUNITY-BASED PARTICIPATORY RESEARCH:

N/A

SHARING OF RESULTS WITH PARTICIPANTS:

Results of the study will not be directly shared with the participants.

SETTING:

All of the research including recruitment of patients and analyzing the data will take place at Northwestern Memorial Hospital

RESOURCES AVAILABLE:

The PI, Co-PI, ECS and GMS have extensive experience in managing blood glucose levels in inpatients at NMH and have published extensively on our experience.

Based on our previous experience, we anticipate that 2 –4 patients per week seen routinely by the ECS and GMS would be appropriate for this study and expect that at least 50% of patients will agree to participate.

The PI and Co-PI plan to devote about 5% of our time to supervising this research and the Fellow Investigator plans to devote 50% of her time to carrying out this research.

All patients will be seen at Northwestern Memorial Hospital. No special facilities are needed. Data analysis will be carried out using the computers and software available to the PI and Co-PI.

All participants will be followed individually by the Endocrinology Consult Service and Glucose Management Service and often will be seen by the hospital Diabetes Educator. These will provide additional medical and psychological support in addition to the Investigators in this study.

All members of the ECS and GMS will be informed about the nature of the study and instructed in how the study will be carried out. The Fellow-Investigator will liason directly with them each day on all participants in the study.

PRIOR APPROVALS:

N/A

RECRUITMENT METHODS:

- We will use patients primarily seen on the Endocrine Consult Service as well as the Glucose Management Service (GMS) who are on once daily dosing of prednisone or methylprednisone
- Consent will be obtained at the initial day of Endocrine or GMS inpatient consult, and then subsequently randomized.
- One group will receive NPH in addition to their current glargine lispro basal/bolus regimen with the addition of steroids. (See Table)
- Another group will continue to receive glargine and lispro; however, their basal and bolus regimens will be increased. (see Table)

NUMBER OF LOCAL PARTICIPANTS:

Proposed sample size : Our study aims to recruit 25 inpatients at Northwestern Memorial Hospital to each study arm for a total of 50 patients in the study.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:

All glucose and demographic information will be stored on anonymized confidential files stored in firewalled FSM computers. A separate file will be kept with a patient number and any identifiable information and stored in the firewalled FSM computers.

Participants will be followed daily by the ECS or the GMS as well as the Fellow Investigator who will be able to address all questions and concerns,

The Research Staff will create a dataset in the Enterprise Data Warehouse so as to obtain access to any stored data on participants.

COMPENSATION FOR RESEARCH-RELATED INJURY:

N/A

ECONOMIC BURDEN TO PARTICIPANTS:

NONE

CONSENT PROCESS:

Consent will be obtained at the initial consult while the patient in inpatient at Northwestern Memorial Hospital. Consent with be obtain by the team members of the GMS or Endocrine Fellows on the ECS.

Adults Unable to Consent/ Cognitively Impaired Adults

Because the goal here is to improve glycemic control with less hyperglycemia and less hypoglycemia than standard methods, it seems reasonable to include adults who are cognitively impaired or who are unable to consent and who have appropriate individuals who can give appropriate assent. Such

appropriate individuals, in order of priority, would be those with durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child. Such assent will be documented on the Consent Form.

PROCESS TO DOCUMENT CONSENT IN WRITING:

Participants will be consented at the initial day of consult. A written document will be provided for signature. (see attached)

Table 1. Continue Standard Basal/Bolus Insulin* and add NPH in units adjusted for Prednisone doses according to the following table:

Prednisone Added (mg/day)	NPH Dose (U/mg Prednisone/day	Amount of total NPH added at top of range	Added total NPH Insulin (U/kg) for 70 kg person
> 80	No additional NPH	51	0.73
61 – 80	0.3	51	0.73
41-60	0.45	45	0.64
21-40	0.6	36	0.51
10-20	1.2	24	0.34

*Standard Basal/Bolus Insulin will be considered either a weight based dose (total daily dose of insulin 0.5 U/kg) or patient's home doses of insulin without adjustment

Table 2. Basal/Bolus Insulin adjusted for Prednisone doses according to the following table:

Prednisone Added (mg/day)	Glargine Dose (U/kg)	Breakfast Novolog Dose (U/kg)	Lunch Novolog Dose (U/kg)	Dinner Novolog Dose (U/kg)
>80	0.30	0.15	0.35	0.40
61-80	0.30	0.15	0.3	0.35
41-60	0.30	0.15	0.25	0.30
21-40	0.25	0.1	0.2	0.25
10-20	0.25	0.1	0.15	0.2
0*	0.25	0.08	0.08	0.08

*standard weight based dose of 0.5 U/kg divided 50/50 into basal (glargine) and prandial insulin divided into 3 premeal doses

Note: Prednisone and IV methylprednisolone will be judged to be equivalent with respect to addition of insulin doses according to above tables.