Comparison of Continuous Subcutaneous Insulin Infusion using Insulin Lispro and Multiple Daily Injections with Insulin Glargine plus Lispro in Type I Diabetics: a randomized study

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A. Study Purpose and Rationale

The Diabetes Control and Complications Trial (DCCT) published in 1993 was a landmark study demonstrating that improved glycemic control with intensive insulin therapy in patients with type I diabetes led to graded reductions in retinopathy, nephropathy, and neuropathy.[1] However, the study did not distinguish between continuous infusion or "pump" therapy and multiple injections. Since this time, many studies have been published comparing insulin pump therapy with multiple daily injections in order to distinguish which produces better blood glucose control. The primary outcome measure most often used in these studies is percentage of glycosylated hemoglobin. A meta-analysis published in 2002 of pump therapy vs. injection therapy compared 12 prospective randomized controlled trials published from 1975 to 2000. [2] The results of this meta-analysis were that glycemic control was better with pump treatment. There have been 3 subsequent trials published in 2001, 2002, and 2003, one of which showed no difference between the two modes of insulin delivery, and the other two favoring pump therapy.[3 4, 5]

In the 15 randomized trials mentioned above, all but 3 used regular insulin in the pump with only 3 using the short-acting analog insulin lispro. Several trials since 1998 have proven insulin lispro to be superior to regular insulin in external pump therapy in terms of both glycemic control and frequency of hypoglycemic episodes.[6] Also, in only 2 of the 15 trials were the patients in the multiple injection group using insulin lispro as their short-acting insulin. As insulin lispro as been shown to more-closely mimic the body's response to a meal in terms of onset and duration of action, it is currently the short-acting insulin of choice among tightly-controlled diabetics.[7] In addition, there have been no studies comparing the pump and injections published to date using insulin glargine in the injection regimen. Insulin glargine is unique among insulin preparations as it has a duration of action of 24 hours with no peak in activity. It has been shown in several clinical trials to be the ideal basal insulin for intensive insulin therapy in type I diabetics using injection therapy.[8, 9]

Therefore, there is currently no data comparing the standard of care for insulin pump therapy using insulin lispro with the standard of care for insulin injection therapy using insulin glargine plus lispro. As it has been shown conclusively that, at all levels of glycosylated hemoglobin above normal there is a benefit of improved glycemic control in terms of reducing the risk of complications, it follows that we should confirm which of these methods provides tighter glucose control. That is the purpose of this study. The hypothesis is that, given the unique pharmacokinetics of insulin glargine, there will be no difference in glycosylated hemoglobin between those diabetics using the pump and those using injections. However, secondary outcomes such as quality of life and frequency of hypoglycemic episodes may also play a role in deciding which method is superior.

B. Study Design and Statistical Analysis

This will be a prospective randomized open-label study to compare the two methods of intensive insulin therapy. Patients will be recruited from the CPMC internal medicine outpatient facilities. Patients will be randomly assigned to either pump or injection therapy. Risk stratification will be done based on college education (some vs. none), age, and gender.

The primary outcome measurement will be HbA1C (%) at the end of the study. The hypothesis is that the two arms will be equivalent with respect to the primary outcome. Using the unpaired t-test and defining "equivalency" as a difference in HbA1C of 0.2% or less, the sample size needed for 80% power is 145 participants in each arm of the study. This was calculated using an estimated standard deviation for HbA1C of 0.6. This SD was obtained from the results of the 2 most recent trials comparing insulin pump therapy with multiple daily injections.

The secondary outcomes measured will be hypoglycemic events and quality of life.

Data will be analyzed using the intention-to-treat principle and continuous criteria will be compared by the t- test. A "negative" study will indicate equivalency among the two groups.

C. Study Procedure

After randomization, each group will undergo an educational session regarding insulin dosing, diet, and exercise. The group randomized to pump therapy will also require training on how to operate and adjust the device. During the initial phase of treatment, patients will be closely monitored by a diabetologist with an outpatient visit at 2, 4, and 8 weeks. They will also be in contact with their diabetologist weekly via the telephone. This will be done in order to further educate the patients and aid them in the fine-tuning of their insulin regimen. After this initial phase, the patients will resume a normal follow-up schedule with outpatient visits every 3 months for a total study duration of 1 year. Insulin regimens will be adjusted based on the results of self-monitoring and by the diabetologist at each visit. At each visit, insulin dose and adverse events will be noted. Patients will keep an electronic log of their daily blood glucose measurements performed before and 2 hours after each meal and at any other time the patient deems necessary. These numbers will be shared with and recorded by the diabetologist at each visit in order to properly adjust insulin regimens and track hypoglycemic episodes. HbA1C will be measured at 8 weeks and at every 3 month follow-up appointment. At the end of the 1 year study, participants will be asked to rate their satisfaction with their mode of insulin delivery.

D. Study Drugs

Insulin lispro is an approved drug routinely used in both external insulin pumps and as an isolated injection using a standard syringe. Insulin glargine is likewise an approved drug routinely used as a once-daily injection. The primary adverse side-effect of all insulin formulations is hypogycemia.

E. Medical Device

The insulin pump to be used is a commercially available device proven to be safe and effective. Patients randomized to receive the pump will be thoroughly educated in the maintenance and upkeep of the device. The primary risks of pump therapy include infection at the site of implantation and pump malfunction.

F. Study Questionnaires

Patients will be asked at the completion of the study if the were very satisfied, satisfied, or unsatisfied with their insulin delivery system and whether or not they planned to continue with their assigned regimen.

G. Study Subjects

Participants in the study will be Type I diabetics over the age of 18. There will be no limitation on duration of diabetes or HbA1C at time of enrollment. Exclusion criteria will include impaired renal function, gastric neuropathy, and BMI>35, all of which could alter either the pharmacokinetics of insulin

or the absorption of dietary nutrients. We would also exclude patients with any severe disease that could interfere with the study including psychological infirmities and alcoholism. The psychosocial factors shown in prior studies to repeatedly correlate with glycemic control are formal education and social support, with occasional studies citing age, gender, smoking, and income as significant variables. [11, 12] For this reason, we will exclude those patients without a support system of family and/or friends. We will also risk-stratify using college education, age, and gender.

H. Recruitment of Subjects

Subjects will be identified in two ways. First, flyers will be posted visible to CPMC employees who may wish to enroll themselves or their friends or family members. Second, internists or diabetologists at CPMC will be made aware of the study via a mailing.

I. Confidentiality

All information obtained during this study will be strictly confidential. The primary investigators and diabetologists will evaluate information obtained during the study. No patient identification will be recorded.

J. Potential Conflict of Interest

None

K. Location of Study

This study will take place at Columbia Presbyterian Medical Center in an outpatient facility.

L. Potential Risks

The risks involved in this study are the same as those involved with using any intensive insulin regimen, namely hypoglycemia. The external pump device also has the risks of pump malfunction (in current models, this is estimated to occur in<1% of all pumps handled correctly and the devices are equipped with an alarm to alert the patient if the pump has ceased to deliver insulin.) and infection at the site of implantation (also <1% if the materials are inserted and changed as directed.)[10]

M. Potential Benefits

The benefit of involvement in this study to the subject is a better understanding of diabetes and an improved control of their blood glucose. They will also receive close medical follow-up by a physician specializing in diabetics. The benefit to the medical community is to demonstrate the optimal mode for glycemic control in type I diabetics.

N. Alternative Therapies

Both therapies used in this trial as well as numerous other insulin regimens are available to all patients.

O. Compensation to Subjects

Study participants will not receive monetary compensation.

P. Costs to Subjects

The costs to the subjects include only time involved in education and medical evaluation.

Q. Minors as Research Subjects

No minors will participate in this study

R. Radiation or Radioactive Substances

This study will not expose patients to radiation or radioactive substances.

S. Refenences

1. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977-86.

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8. Heinemann et al. Time-action profile of the long-acting insulin analog glargine in comparison with those of NPH and placebo. *Diabetes Care* 2000; 23: 639.

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10. Lenhard, MJ, Reeves, GD. Continuous subcutaneous insulin infusion: a comprehensive review of insulin pump therapy. *Arch Intern Med* 2001; 161:2293.