Detemir vs Glargine: Comparison of Inpatient Glycemic Control

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Context: Hyperglycemia in the hospital setting is associated with increased morbidity and mortality. In an attempt to cut costs, some hospitals implement policies to substitute all glargine orders with detemir.

Objective: To examine how the substitution of glargine with detemir affects inpatient blood glucose control.

Methods: Medical records were retrospectively analyzed to investigate the effect of a hospital formulary change at a semi-urban underserved hospital that substituted detemir for glargine on a 1:1 dosing basis. The study evaluated blood glucose control from September 6, 2015, to September 5, 2016, before substitution and from September 6, 2016, to September 5, 2017, after the substitution began. Patients were included in the study if they were older than 18 years, received glargine before admission, and had type 1 or 2 diabetes mellitus. Patients were excluded if they were pregnant, did not receive long-acting insulin, or lacked regular blood glucose testing. The medical records were analyzed for mean glucose levels, hypoglycemic events, and short-acting insulin administration amounts.

Results: A total of 318 patients met criteria and were included in the retrospective analysis—134 patients received detemir and 184 patients received glargine. The mean glucose levels in the morning were 133.8 mg/dL for patients receiving detemir and 145.8 mg/dL for patients receiving glargine (95% CI, 126.972-140.753; *P*=.013). The mean blood glucose levels in the afternoon were 171.6 mg/dL for patients receiving detemir and 172.1 mg/dL for patients receiving glargine (95% CI, 162.955-180.344; *P*=.938). The mean blood glucose levels in the evening were 162.5 mg/dL for patients receiving detemir and 163.3 mg/dL for patients receiving glargine (95% CI, 153.654-171.315; *P*=.897). The mean blood glucose levels at night were 176.1 mg/dL for patients receiving detemir and 174.7 mg/dL for patients receiving glargine (95% CI, 167.797-184.474; *P*=.788). No significant difference in sliding scale insulin was required between the patient groups (0.16 U/kg insulin aspart in detemir group vs 0.18 U/kg aspart in glargine; 95% CI, 0.154-0.189; *P*=.297). There was no significant difference between the patient groups in regard to hypoglycemic events (45% glargine vs 49% detemir; *P*=.59).

Conclusion: Substituting detemir for glargine did not adversely affect inpatients' blood glucose control.

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Diabetes mellitus affects more than 30.3 million people in the United States and more than 7.2 million hospitalized patients.[1] Uncontrolled hyperglycemia is associated with increased morbidity and mortality in hospitalized patients.[2] To combat this problem, hospitals use basal insulin and bolus insulin regimens to keep blood glucose controlled. Most hospitals use either detemir or glargine as the sole formulary basal insulin. Is it safe to assume that these insulin types in the hospital setting are interchangeable?

Detemir is a long-acting basal insulin that was approved by the US Food and Drug Administration in 2005. It is a recombinant insulin that differs from human insulin by the addition of a fatty acid group at B29, which slows systemic absorption of detemir from the injection site.[3] The slow systemic absorption causes detemir to have a longer duration of action and a more even response curve. Although detemir is approved for once-daily dosing, it does not always provide 24-hour basal coverage. Pharmacodynamic studies submitted to the US Food and Drug Administration show a dose-dependent time of action. A detemir dose of 0.1 U/kg had a duration of action of 5.7 hours, 0.4 U/kg had a duration of action of 19.9 hours, 0.8 U/kg had a duration of action of 22.7 hours, and 1.6 U/kg had duration of action of 23.2 hours.[4]

On the other hand, the basal glargine can last for more than 24 hours.[5] Glargine is also a recombinant insulin, but it varies from human insulin at the A21 position where the amino acid asparagine is replaced by glycine and 2 arginines are added to the C-terminus of the B-chain. After injection into the subcutaneous tissue, microprecipitates are formed and small amounts of glargine are slowly released.[5] This results in a relatively constant, non–dose-dependent concentration/time profile over 24 hours without a pronounced peak.[5] However, when glargine is compared with detemir in clamp studies, several patients receiving glargine did not respond to the insulin treatment. Koehler et al[6] found a 33% nonresponse rate to glargine, and Heinemann et al[7] found a 23% variation in response to glargine between patients.

Detemir and glargine have been compared head-to-head several times in the outpatient setting. Another outpatient study conducted by Rosenstock et al[8] randomly assigned 542 patients with type 2 diabetes to either detemir or glargine in addition to their oral regimen. This study found a similar hemoglobin A_{1c} (HbA_{1c}) reduction of 1.5% and a similar 52-week baseline HbA_{1c} of 7.2% and 7.1% for detemir and glargine, respectively. However, 55% of the patients receiving detemir required doses twice per day.[8] A double-blind study done by King[9] in the outpatient setting found similar glycemic control between glargine and detemir. However, this study[9] had a small sample size of 26 patients.

A meta-analysis by Rys et al[10] of outpatient glucose control compared detemir, glargine, and NPH (neutral protamine Hagedorn) insulin. This study found that detemir and glargine created similar glucose level control and were superior to NPH insulin. However, trials done in an outpatient setting may not accurately reflect the difference in blood glucose control between detemir and glargine in the inpatient setting because of physiologic changes that occur, such as inflammation, fever, hypoalbuminemia, medications, and changes in serum hormone levels.

A few studies have been conducted in hospital settings that compare detemir to glargine. Zhang et al[11] performed a crossover study of 42 patients in which half were administered glargine followed by detemir and half were administered the opposite, detemir followed by glargine. They found no significant difference in blood glucose control between the groups.[11] A retrospective study by Davis et al[12] analyzed 188 hospitalized patients receiving glargine or detemir. The study found that a higher percentage of patients achieved the blood glucose reading goal of less than 180 mg/dL when they received glargine compared with the patients who received detemir.[12] These studies have conflicting findings and indicate a need for further research in this area. Thus, we examined how changing basal insulin from glargine to detemir affects inpatients' blood glucose control.

Methods

This retrospective study analyzed the medical records of hospitalized patients with diabetes mellitus who received glargine prior to going to the hospital. The study was conducted at a 350-bed, Level II trauma facility in southern Colorado. The hospital implemented a formulary change in which the generic detemir replaced all glargine orders starting September 5, 2016. People with diabetes using outpatient glargine therapy were switched to detemir on a 1:1 dosing basis on hospital admission. The study was approved by the Parkview Health Institutional Review Board. All patient data were protected in accordance with the Parkview Health Institutional Review Board.

This study analyzed blood glucose control of 2 different treatment groups: patients admitted before the hospital formulary change and patients admitted after the change. The first period reviewed was September 6, 2015, to September 5, 2016. During this period, all patients taking glargine outpatient therapy were treated with glargine during inpatient therapy. The second period reviewed was September 6, 2016, to September 5, 2017. During this period, patients who were using glargine as an outpatient were switched to detemir as an inpatient on a 1:1 dosing basis. The insulin use data for these periods were collected from a medical record review. The amount of basal insulin administered to patients was recorded and converted to units per kilogram to adjust for differences in patient weight.

To observe the effect of inpatient basal insulin administration, glucose data collection began after the first midnight of a patient's admission. Glucose readings were collected and analyzed 4 times per day as follows: morning before breakfast (between 5:00 AM and 10:00 AM), afternoon before lunch (between 10:01 AM and 3:00 PM), evening before dinner (between 3:01 PM and 8:00 PM), and night before bed (between 8:01 PM and 1:00 AM).

Additionally, the effect of bolus insulin aspart was collected and analyzed to look for any changes in bolus insulin used. The insulin aspart dose data were averaged, adjusted for weight in kilograms, and studied during the same time frames as above.

Patients were included in the study if they were older than 18 years, admitted to the hospital, had type 1 or 2 diabetes mellitus, and taking glargine insulin prior to hospital admission. Patients were then excluded from the study if they were pregnant, discharged in less than 24 hours, not administered basal insulin, had an insulin pump for administration of insulin, or did not have glucose checks for the above indicated periods. Patients were also excluded if they were admitted for more than 14 days, as this study aimed to analyze outcomes from an acute hospital stay. Intensive care unit patients were not included in the study; however, they were included after being transferred to the medical unit. Patients using corticosteroids and patients with chronic kidney disease were not excluded from the study.

The primary clinical end point was the mean glucose control between the glargine group and detemir group at the 4 periods defined previously. The secondary end points included hypoglycemic events between groups and differences in bolus insulin needed.

A 2-tailed *t* test was used to compare study variables between the glargine group and the detemir group. The data were deemed statistically significant if the *P* value was less than .05. An Anderson-Darling test was used to prove normal distribution of data. An F test was performed to find whether the variance was similar between the 2 variables. The CI was calculated at 95%.

All data had a normal distribution by Anderson-Darling test at $P=.05$ except the nighttime blood glucose, which was not rated as a normal distribution ($P=.134$). The distribution does not affect the data and verified the null hypothesis because no significant difference was found in the nighttime blood glucose between the 2 groups. All of the blood glucose data and insulin aspart data had equivalent variance by F test except the morning insulin aspart dose, which did not have equal variance by F test. To adjust for the unequal variance, a *t* test was performed for the morning insulin aspart data.

Results

A total of 207 patients were excluded from the final analysis; 162 patients did not meet the inclusion criteria and 45 patients were excluded because of incomplete data collection. A total population of 318 patients were analyzed (175 men and 143 women): 184 patients received glargine from September 6, 2015, to September 5, 2016, and 134 patients received detemir from September 6, 2016, to September 5, 2017 (**Table 1**).

The patients in the detemir group had statistically lower fasting morning blood glucose levels than patients in the glargine group (**Table 2**). The mean morning glucose level in the detemir group was 133.9 mg/dL compared with 145.8 mg/dL in the glargine group (95% CI, 126.972-140.753; *P*=.013). The patients receiving detemir seemed to require lower doses of sliding scale insulin aspart in the morning than the patients who received glargine. However, analysis showed this finding was not statistically significant (0.04 U/kg detemir vs 0.05 U/kg glargine, 95% CI, 0.032-0.052; *P*=.114).

Table 1.
Characteristics of Hospitalized Patients With Diabetes Using Glargine and Detemir for Glycemic Control (N=318)

Variables	Detemir (n=134)	Glargine (n=184)
Men, No. (%)	76 (56.7)	99 (54)
Women, No. (%)	58 (43.3)	85 (46)
Age, mean (SD), years	70.91 (11.7)	68.83 (10.3)
Length of stay, mean (SD), d	4.83 (4.3)	4.71 (2.9)
Weight, mean (SD), kg	97.1 (27.82)	96.03 (31.22)
No. with type 1 diabetes mellitus	1	6
Episode of blood glucose <70 mg/dL, No. (%)[a]	66 (49)	85 (46)
Episode of blood glucose <40 mg/dL, No. (%)	3 (2)	4 (2)

[a] Significant at *P*<.05

The afternoon glucose readings were similar between detemir and glargine. The mean blood glucose level was 171.6 mg/dL for the detemir group vs 172.1 mg/dL for the glargine group (95% CI, 162.955-180.344; *P*=.938). The afternoon insulin aspart dose needed was lower in the detemir group but not by a significant margin (0.05 U/kg detemir vs 0.06 U/kg glargine, 95% CI, 0.043-0.061; *P*=.393).

The evening glucose control was also similar between the detemir and glargine groups. The mean detemir glucose reading was 162.5 mg/dL and glargine was 163.3 mg/dL (95% CI, 153.654-171.315; *P*=.897). The amount of sliding scale insulin aspart required in the evening was also not different between the 2 groups (0.05 U/kg detemir to 0.05 U/kg glargine, 95% CI, 0.039-0.055; *P*=.306).

The blood glucose control at night was also very similar between detemir and glargine. The mean detemir glucose reading was 176.1 mg/dL, which was similar to the mean glargine glucose reading of 174.7 mg/dL (95% CI 167.797-184.474; *P*=.788). The amount of insulin aspart given at night was also not statistically different between the detemir and glargine groups (0.019 U/kg for detemir and 0.017 U/kg for glargine, 95% CI 0.013-0.026; *P*=.686). The **Figure** provides a visual presentation of patients' mean glucose readings throughout the day.

Overall, there was no statistical difference in the dosage requirements of the detemir and glargine groups. The mean detemir dose was 0.39 U/kg compared with 0.45 U/kg of glargine (95% CI 0.348-0.437; *P*=.067). Also, the percentage of patients receiving twice per day detemir was not significantly different from those receiving twice per day glargine: 34.3% for detemir and 33.2% for glargine. This also held true for the dosage of insulin aspart used between the 2 groups (the detemir group required 0.16 U/kg of insulin aspart vs the glargine group, which required 0.18 U/kg of insulin aspart, 95% CI, 0.154-0.189; *P*=.297)

In addition to similar dosing requirements, there was no significant difference in hypoglycemic events

Table 2.
Insulin Dosing in Hospitalized Patients With Diabetes Mellitus (N=318)

Variables	Detemir	Glargine	*P* Value[a]
Glucose, Mean (SD), mg/dL			
Morning	133.9 (40.3)	145.8 (43.2)	.013
Afternoon	171.6 (50.9)	172.1 (53.5)	.938
Evening	162.5 (51.7)	163.3 (52.7)	.897
Night	176.1 (48.8)	174.7 (46.2)	.788
Mean Basal Insulin Dose, U/kg	0.39	0.45	.067
Patients With Twice Daily Basal Insulin Dose, No. (%)	45 (34)	62 (33)	NA
Mean Aspart Dose, U/kg			
Morning	0.04	0.05	.114
Afternoon	0.05	0.06	.393
Evening	0.05	0.05	.306
Night	0.02	0.02	.686

[a] Significant at $P<.05$.

between detemir and glargine. In the detemir group, 49% of the patients had a hypoglycemic event (blood glucose <70 mg/dL) vs 46% in the glargine group ($P=.59$). No statistically significant difference in length of stay or age was observed between the 2 groups.

Discussion

In this retrospective analysis we discovered no statistically significant difference between detemir and glargine blood glucose control. The detemir group had statistically significant lower blood glucose readings in the morning but had comparable glucose readings to glargine at all other readings. The comparable readings were demonstrated without having increased hypoglycemic events.

Both treatment groups were found to be similar enough to make this analysis accurate. The patients had similar baseline statistics, with similar lengths of stay, age, insulin aspart use, and percentage receiving twice daily basal insulin. Therefore, it is likely that observed differences between the 2 groups were attributable to either detemir or glargine use.

The concern with switching formularies from glargine to detemir was that detemir has a shorter length of action and would cause elevated evening blood glucose levels. However, we found that evening

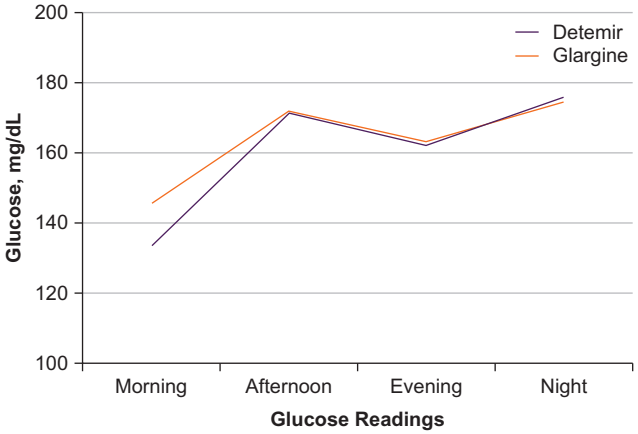

Figure.
The mean glucose readings of hospitalized patients receiving detemir or glargine throughout the day.

glucose elevation did not occur. Also, the similar afternoon, evening, and night glucose control between the detemir and glargine groups was not artificially corrected by the amount of short-acting insulin aspart given, as there was no statistically significant difference in the use of short-acting insulin aspart administered.

Detemir has been demonstrated to have a more peaked curve of effect than glargine and could be the cause of the decreased morning blood glucose levels found in the detemir group. Although detemir led to a lower overall morning blood glucose level, it did not cause an increase in hypoglycemic events or other adverse outcomes. This analysis implies that switching glargine to detemir on a 1:1 basis improves morning blood glucose control without causing more hypoglycemic events.

However, this study has several limitations. The data were taken from a review of patient medical records, which limits the data available for review. The data are also unable to take into account differences in nursing staff and hospital physicians between the 2 sets of patients, which can introduce bias into the data. The data in this study are also limited owing to lack of masking between treatment groups. This problem is less likely to affect patient outcomes because detemir has been around since 2005 and is not likely to be thought of by patients as an experimental therapy or new therapeutic regimen. This change is not likely to introduce bias to the study and instead can provide guidance to hospitals considering similar changes to their formularies. It should also be noted that the hospital relied heavily on basal insulin for blood glucose control, with basal insulin making up to 71% of total daily insulin doses in the detemir group and 71.5% of total daily insulin doses in the glargine group. This heavy reliance on basal insulin makes it less likely that bolus insulin affected the results.

For practical application, it is necessary to consider the patient population the data were generated from. The data may not be applicable to patients in an outpatient setting because patients who are acutely ill may have differences in their absorption of long-acting insulin because of acute medical issues such as inflammation. The study also excluded patients in the intensive care unit; therefore, the data are not likely to be applicable to this population.

The study also may not be applicable to the opposite question of transitioning patients from detemir to glargine. All of the patients were taking glargine prior to hospital admission, which indicated that they were likely able to tolerate and respond appropriately to glargine. The inclusion criteria may thus have excluded nonresponders to glargine from our study and may be significant as some studies put the nonresponse rate to glargine at 33%.[7]

Conclusion

Substituting detemir for glargine on admission to the hospital does not negatively affect blood glucose control. It did not cause an increase in sliding scale insulin dosage requirements or an increase in hypoglycemic events. This study provides evidence that patients can be safely switched from glargine to detemir in the hospital setting.

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Author Contributions

Drs Capson and Avanesyan provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Drs Capson and Cade drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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