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Basal Insulin Use in the Non–Critical Care Setting: Is Fasting Hypoglycemia Inevitable or Preventable?

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In an effort to improve glycemic control in inpatients in a large urban academic medical center, we set out to examine risk factors for hypoglycemia associated with basal insulin usage when blood glucose (BG) levels are above target (180 mg/dL). Guidelines recommend use of insulin to prevent hyperglycemia in hospitalized patients,[1,2] and randomized trials have shown that regimens that include basal insulin are more effective than rapid-acting insulin alone.[3-5] These trials also show that basal insulin increases the rate of hypoglycemia, a fact that likely contributes to clinical inertia on the part of prescribers. Although basal insulin use in inpatients yields significant clinical benefits, it is important to acknowledge and manage the associated risk of iatrogenic hypoglycemia.

To that end, we performed a retrospective cohort study using data extracted from the electronic medical record system at a large urban academic medical center. Eligible patients were adults with nonobstetric and non-ICU admissions lasting over 24 hours for whom basal insulin was ordered. The order for basal insulin was the exposure. Insulin glargine was the on-formulary insulin at our institution, and virtually all basal insulin exposures were insulin glargine. Basic demographics and the previous 48 hours of point-of-care BG measurements were covariates. The outcome was fasting hypoglycemia, defined as a BG <70 between 4:00 AM and 10:00 AM. The covariates were used to construct a hypothesis-based multivariable prediction model with predefined training and validation sets.

A total of 3321 admissions between January 1, 2010, and January 1, 2012, were eligible. When basal insulin was ordered, the risk of fasting hypoglycemia per day increased from 1.1% (95% CI 0.9%-1.5%) to 3.2% (95% CI 2.9%-3.5%), with a cumulative probability of 10.7% (95% CI 9.7%-11.8%) for an episode during the 5 days after basal insulin initiation. The rate of nonfasting hypoglycemia did not increase. For patients exposed to basal insulin, low-normal fasting BG (70-99 mg/dl) was associated with an odds ratio of 4.9 (95% CI 3.8-6.2) for next-day fasting hypoglycemia. This corresponded a 10% absolute risk (compared to 2% if fasting BG was > 99), predicting 35% of events with a specificity of 90%. Despite this, when low-normal fasting glucose was present, basal insulin was kept at the same dose in 86% of cases, and titrated up in 4%. A hypothesis-based multivariable prediction model incorporating additional variables (Table 1) had an area under the receiver operator curve of 0.76 in the validation cohort, with a positive predictive value of 16% for the highest-risk decile.

While the original intention of this study was to develop and validate a multivariable prediction algorithm for fasting hypoglycemia, one striking finding is that a low-normal morning blood sugar (70-99 mg/dl) is by itself an effective predictor of hypoglycemia the next morning. This is consistent with previous reports that hypoglycemic episodes in general are often preceded by low-normal glucose levels,[6] and with guidelines that low-normal glucose should prompt insulin dose reduction.[1]

However, this study is the first to quantify the risk associated with low-normal fasting glucose in the setting of basal insulin use, and to show that many providers do not follow common-sense titration practices. These findings support the need for provider education on inpatient insulin titration guidelines. More complex prediction algorithms may be useful, but the most cost-effective way to expand safe use of basal insulin may be provider education about the clinical importance of low-normal fasting BG.

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Table 1. Multivariable Odds Ratios for Next-day Fasting Hypoglycemia for Inpatients Receiving Basal Insulin.

	Odds ratio	95% CI lower	95% CI upper	*P* value
Sex (female)	1.01	1.00	1.01	.147
Age (10 year)	1.01	0.81	1.26	.929
Basal insulin dose (units)				
<10 units	ref			
10-15 units	1.15	0.80	1.66	.444
15-25 units	1.32	0.97	1.79	.078
>25 units	1.94	1.48	2.54	<.001
Fasting glucose (mg/dl)				
<100	7.15	3.73	13.71	<.001
100-150	2.66	1.40	5.06	.003
150-250	1.77	0.94	3.32	.077
>250	ref			
Bedtime glucose (mg/dl)				
<100	2.62	1.69	4.06	<.001
100-150	1.91	1.32	2.75	<.001
150-250	1.18	0.85	1.65	.318
>250	ref			
Lowest daytime (mg/dl) glucose				
<100	4.43	2.47	7.97	<.001
100-150	2.68	1.51	4.76	<.001
150-250	1.99	1.13	3.49	.017
>250	ref			
Prior overnight decline in blood glucose (mg/dl)				
No decline or increase	ref			
0-50	0.93	0.64	1.33	.676
50-100	1.50	1.05	2.15	.027
>100	1.75	1.21	2.54	.003

All variables shown were included in a logistic regression model as independent variables. All glucose values are point-of-care results in mg/dl.

Abbreviations

AUC, area under the receiver-operating curve; BG, blood glucose; BMI, body mass index; EMR, electronic medical record; NPV, negative predictive value; PPV, positive predictive value.

Declaration of Conflicting Interests

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