LETTER TO THE EDITOR

Analysis of Continuous Glucose Monitoring Data to Assess Outpatient Closed-Loop Studies: Considerations for Different Sensors

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Dear Editor:

CLOSED-LOOP SYSTEMS HAVE BEEN ASSESSED in many inpatient studies under standardized and controlled conditions but are rarely evaluated in outpatient settings. In most outpatient settings, frequent reference glucose measurements to assess the performance of closed-loop systems are impractical, and continuous glucose monitoring (CGM) could be used alternatively to estimate study outcomes. However, the ability of CGM to provide unbiased outcomes might be hindered by its suboptimal accuracy, and certain mathematical transformations of CGM data might be needed before calculating the end points. Hovorka et al.¹ proposed a stochastic modification for CGM readings to provide an unbiased assessment for outpatient closed-loop studies.

The authors based their analysis on data from the Navigator[®] CGM system (Abbott Diabetes Care, Alameda, CA). Their work was an important first step tackling the methodological issues in assessing outpatient studies but is limited by the usage of only one CGM system. We assessed whether their findings generalize to the Medtronic Sof-Sensor[®] glucose sensor (Medtronic Diabetes, Northridge, CA). We performed secondary analysis on data from two randomized trials (one published² and one still being conducted) comparing conventional pump therapy with dual-hormone closed-loop delivery driven by the Sof-Sensor. We analyzed data from 23 subjects and included only nighttime data (10 p.m.–7 a.m.) to allow comparison with the work of Hovorka et al.¹

Similar to Hovorka et al.,¹ the unmodified CGM resulted in overestimation of the time spent in target range with closed-loop therapy ($P=0.005$) but not with the conventional pump therapy ($P=0.22$) (Table 1). This is due to, as discussed by Hovorka et al.,¹ using the sensor *both* for driving the algorithm and for calculating the end points. In addition, our unmodified CGM resulted in significant underestimation

($P=0.001$) of the time spent in hyperglycemia during closed-loop therapy, reflecting that this specific sensor under-reads in the hyperglycemia range.^{2,3}

We assessed whether the stochastic CGM would eliminate bias, similar to what was reported with the Navigator CGM system.¹ The overestimation of time spent in target range and the underestimation of time spent in hyperglycemia were unfortunately still present (Table 1). Moreover, the stochastic CGM resulted in an additional bias in time spent in the hypoglycemia range (overestimation values, Table 1).

Our studies indicate that the Sof-Sensor under-reads in the hyperglycemic range but not in the nonhyperglycemic ranges,² comparable to observations by others.³ Reflecting these unique characteristics, we proposed a modified CGM that maps the target range from 4.0–8.0 mmol/L in the reference glucose domain to 4.0–7.0 mmol/L in the CGM domain. We adopted this 1 mmol/L difference from analysis of CGM–YSI pairs.² This corrected CGM would alter the estimation of times spent in target range and hyperglycemia but not hypoglycemia. This corrected CGM resulted in unbiased estimates for all the three end points (Table 1).

We also compared the paired difference (closed-loop–conventional pump therapy) when measured using plasma glucose data with that when measured using the unmodified CGM data, stochastic CGM data, and the corrected CGM data (Table 1). It is interesting that all CGM methods resulted in similar conclusions compared with the plasma glucose data ($P>0.05$). This suggests that if the paired difference is considered, then no transformation for CGM data is necessary, and raw data may provide unbiased estimates.

CGM can be used as an outcome measure in closed-loop trials,⁴ but methodological hurdles remain to be tackled. Hovorka et al.¹ proposed a stochastic CGM transformation that led to unbiased estimates with the Navigator system but

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TABLE 1. COMPARISON BETWEEN OUTCOME MEASURES OF CLOSED-LOOP DELIVERY AND CONVENTIONAL PUMP THERAPY CALCULATED USING REFERENCE GLUCOSE AND UNMODIFIED, STOCHASTIC, AND CORRECTED CONTINUOUS GLUCOSE MONITORING

	<i>Plasma glucose</i>	<i>CGM</i>		
		<i>Unmodified</i>	<i>Stochastic^a</i>	<i>Corrected^b</i>
% of time below target				
Closed-loop	0.6 (3)	1.9 (5)	3.7 (5) ^c	1.9 (5)
Insulin pump	13.7 (19)	16.7 (29)	19 (26)	16.7 (29)
Paired difference	– 13 (20)	– 14 (29)	– 15 (27)	– 15 (29)
% of time in target				
Closed-loop	58 (29)	71 (23) ^c	67 (20) ^c	56 (27)
Insulin pump	45 (31)	55 (30)	53 (23)	40 (26)
Paired difference	12 (38)	16 (30)	14 (23)	16 (26)
% of time above target				
Closed-loop	42 (31)	27 (23) ^c	29 (21) ^c	42 (28)
Insulin pump	41 (39)	28 (29)	29 (25) ^c	43 (32)
Paired difference	1 (43)	– 1 (27)	0 (23)	– 1 (30)

Data are mean (SD) values. Target range is defined between 4.0 and 8.0 mmol/L. The paired difference value is that for closed-loop minus that for conventional pump therapy.

^aThe stochastic continuous glucose monitoring (CGM) is defined by Hovorka et al.¹ and assumes an unbiased 15% measurement error.

^bThe corrected CGM maps the target range from 4.0–8.0 mmol/L in the reference glucose domain to 4.0–7.0 mmol/L in the CGM domain.

^c $P < 0.05$, indicating a statistically significant difference compared with end points measured using plasma glucose data.

not, in our data, with the Medtronic Sof-Sensor. Based on the unique characteristics of the Sof-Sensor, we proposed an alternative CGM transformation that led to unbiased estimates. Caution needs to be taken when applying these methods, and considerations for different CGM systems need to be taken.

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