Continuous Glucose Monitoring (CGM) Reveals Undertreated Hypoglycemia in Patients with Congenital Hyperinsulinism

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INTRODUCTION & BACKGROUND

Congenital Hyperinsulinism (HI) is the most frequent cause of severe, persistent hypoglycemia in children (Lord & De León). Monogenic hyperinsulinemic hypoglycemia: current insights into the pathogenesis and management, 2013. Patients experience a high prevalence of neurodevelopmental abnormalities (26-46%) regardless of the duration of the hyperinsulinism or treatment modality (Lord & De León-Crutchoff). Neurodevelopmental Outcomes, 2019. The use of currently available treatments, 28% of patients (Figure 1) report continued hypoglycemia according to the HI Global Registry 2020 Annual Report (Hood, et al., 2020).

Figure 1: Percent of patients reporting at least daily hypoglycemia, by SOC.

Patients with Type 1 diabetes mellitus (T1DM) also experience adverse neurocognitive outcomes as a result of hypoglycemia; therefore, the intervention goals for T1DM may be viewed as a useful and robustly-studied analog to congenital HI. The Advanced Technologies and Treatments for Diabetes (ATTD) expert panel provided consensus guidelines for recommended time in range using CGM (Figure 1), notably a target time in hypoglycemia (< 70 mg/dL (3.9 mmol/L), < 60 mg/dL (3.3 mmol/L), or < 50 mg/dL (2.8 mmol/L)).

There is a lack of analogous published literature and guidelines in congenital HI. Utilizing analogous time in range such as T1DM, additional research is needed to further characterize and to quantify hypoglycemia in patients with congenital HI in order to guide goals of care and future therapy development.

A two-week observational study was conducted in congenital HI patients ages 2 years and older, recruited randomly from the Congenital Hyperinsulinism International community, using CGM (Dexcom G4®). Hypoglycemic thresholds in this study were defined as <70 mg/dL (3.9 mmol/L), <60 mg/dL (3.3 mmol/L), or <50 mg/dL (2.8 mmol/L).

RESULTS

• Twenty-two patients ages 2-36 years old (Males:9, Females:13) with CHI of various ages and etiologies participated in this study.
• Fifteen patients were receiving at least one SOC therapy which included:
  - 11 (50%) on diazoxide,
  - 4 (18%) on octreotide,
  - 7 (32%) managed by other means (continuous enteral dextrose, glucagon, and/or diet).
• 5 patients were also post-pancreatectomy (< 50% to > 95% removal).
• Time in hypoglycemia observed is outlined in Table 1.

The results equate to an average of:
  - Over 2.5 hours per day in hypoglycemia for all participants
  - Nearly 3.5 hours per day for those 2-6 years old
  - Patients taking SOC therapies experienced a similar magnitude of hypoglycemia.

CONCLUSION & DISCUSSION

Persistent hypoglycemia places patients with congenital HI at risk for adverse clinical outcomes including developmental and neurocognitive deficits. The American Diabetes Association and the Endocrine Society management guidelines for those diagnosed with congenital HI recommend maintenance of blood glucose > 70 mg/dL (Thorton, et al., 2015) to the extent possible. As evidenced by the CGM results of this study, patients with congenital HI, even on available SOC therapies, had substantial continued hypoglycemia, thus missing the recommended therapeutic goal. This was especially true for the younger patients in this study, who are also at the greatest risk of neurocognitive sequelae due to cumulative hypoglycemia. Therapeutic goals for improvement of overall or cumulative hypoglycemia, based on the extent or duration of time below desired thresholds, are not specified in the published guidelines. This observational study demonstrates that while on the current available standard of care, study participants experienced more than three times the hypoglycemia in a neurologically vulnerable age group than is recommended in the T1DM population. More effective treatments are needed to minimize hypoglycemia to achieve glucose normalization.

In the evaluation of potential new therapies or combination of therapies for congenital HI, better understanding of the baseline magnitude of time in glycemic ranges and a quantitative standard for clinically meaningful glycemic targets are needed. While the authors acknowledge historical device inaccuracy in the lower glucose ranges, significant technologic advancement in CGM and monitoring algorithms continue to be made. Qualitatively, the primary therapeutic goal for safe and effective glycemic management would be to increase the time-in-range while reducing the time-below-range as much as is achievable. Until standardized treatment goals are developed for congenital HI, it may be appropriate to extrapolate and utilize relative hypoglycemia improvements and treatment targets from clinical trials in diseases where hypoglycemia is common, such as T1DM. The results of this study documents residual hypoglycemia beyond what can be detected by intermittent measurement of blood glucose via point of care monitors, further demonstrating that CGM should have an important adjunctive role in the monitoring of congenital HI patients toward to be-determined standardized glycemic targets.

Table 1. Time in hypoglycemia (< 70 mg/dL) by observation week.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 22</td>
<td>1165</td>
<td>154</td>
</tr>
<tr>
<td>Age 7-10 yr 4</td>
<td>770</td>
<td>567.1</td>
</tr>
<tr>
<td>Age 11-15 yr 2</td>
<td>1432.5</td>
<td>1417.4</td>
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<tr>
<td>Age 16 yr 4</td>
<td>1070</td>
<td>1194.8</td>
</tr>
<tr>
<td>Subgroup on SOC 15</td>
<td>1269.3</td>
<td>973.6</td>
</tr>
<tr>
<td>Age 2-5 yr 4</td>
<td>770</td>
<td>567.1</td>
</tr>
<tr>
<td>Age 6-7 yr 2</td>
<td>1432.5</td>
<td>1417.4</td>
</tr>
</tbody>
</table>

*calculated based on 10080 minutes/week

References: