When NICE is Not Nice: Performance of Two ICU Glycaemic Control Protocols

Vincent Uyttendaele1, Jennifer Dickson1, Kent Stewart2, Geoff Shaw2, Thomas Desaive3, J. Geoffrey Chase2
1Centre of Biomedical Engineering, University of Canterbury, New Zealand
2Department of Intensive Care, Christchurch Hospital, New Zealand
3GAA science group, University of Liège, Belgium

Objectives

Glycaemic control using insulin therapy has shown clinical benefits and improved outcomes in critical care. However, the international multi-centered NICE-SUGAR trial have failed to reproduce these results. This study compares the table-based NICE-SUGAR and model-based STAR protocols and assess their relative capability to achieve safe, effective control for all patients. The level of compliance is also tested using NICE-SUGAR published results.

Methods

Clinical Data

Validated virtual patients (n=443) are used to simulate glycaemic outcomes from the NICE-SUGAR and STAR protocols, and are compared with reported clinical data [1].

Protocols

- **NICE-SUGAR** is a table-based protocol targeting 4.5-6.0 mmol/L (intensive therapy). There are no guidelines regarding nutrition. The original protocol measures hourly.
- **STAR** is a model-based protocol modulating both insulin and nutrition. The STAR target band is 4.4-8.0 mmol/L, and enteral feed is modulated between 30-100% goal feed.
- **NICE-SUGAR 3-hours (NS-3H)** was created to approximate the number of measurements reported clinically, using 3 hourly measurements if BG is within the 4.5-10 mmol/L band, unless BG decreased rapidly.

As NICE-SUGAR does not modulate nutrition, 100% STAR goal feed was used for all patients.

Performance and safety analysis

- **Performance is assessed by:**
  - % time in the 4.4-8.0 mmol/L
  - Per-patient mean blood glucose (BG) level
- **Safety is evaluated by:**
  - Number of severe hypoglycaemic events (BG < 2.2 mmol/L)
  - % BG < 4.0 mmol/L

STAR vs. NICE-SUGAR (per protocol):

- **STAR provides better performance** than NICE-SUGAR, with higher % BG in 4.4-8.0 mmol/L range (90.7% vs. 78.3%), and tighter median [IQR] per-patient BG (6.2 [5.9, 6.6] vs. 6.5 [5.9, 7.6]).
- **STAR is safer** with 5 (1%) vs. 10 (2.5%) patients experiencing severe hypoglycaemia, and 1.2% vs. 3.1% BG < 4.0 mmol/L.
- **STAR has lower workload**, with ~12 measurements per day where NICE-SUGAR averages ~25.

NICE-SUGAR clinically reported vs. NS-3H:

- NS-3H resulted in a mean ~10.5 measurements per day, matching better the reported value of 9.4.
- NS-3H safety and per-patient performance were similar to that reported clinically (mean BG (SD) 6.6 (1.9) vs. 6.4 (1.0) mmol/L with 6% of patient experiencing severe hypoglycaemia.

Compliance:

- The reported 9.4 measurements per day does not match the expected ~25 as per protocol, showing clearly the poor compliance of the original NICE-SUGAR study.

Results

Simulation results are summarised in Table 1 and Figure 1.

<table>
<thead>
<tr>
<th>Table 1 – Simulation results summary and recorded clinical outcomes NICE-SUGAR</th>
<th>NICE-SUGAR</th>
<th>NS-3H</th>
<th>STAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patient receiving insulin</td>
<td>97.2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Average measurement per day</td>
<td>~9.4</td>
<td>~25</td>
<td>~105</td>
</tr>
<tr>
<td>Mean insulin dose (SD) L/day</td>
<td>50.2 (38.1)</td>
<td>138 (100)</td>
<td>103.6 (84.7)</td>
</tr>
<tr>
<td>Mean resampled BG (SD) mmol/L</td>
<td>6.4 (1.0)</td>
<td>6.4 (1.9)</td>
<td>6.6 (1.9)</td>
</tr>
<tr>
<td>Median (IQR) per-patient mean BG (mmol/L)</td>
<td>/</td>
<td>6.5 (5.9, 7.6)</td>
<td>6.8 (6.1, 7.8)</td>
</tr>
<tr>
<td>% BG in 4.4-8.0 mmol/L</td>
<td>/</td>
<td>[5.4 - 10.3]</td>
<td>[5.6 - 10.4]</td>
</tr>
<tr>
<td>% BG &lt; 4.0 mmol/L</td>
<td>/</td>
<td>78.3</td>
<td>77.5</td>
</tr>
<tr>
<td>% BG &gt; 4.0 mmol/L</td>
<td>/</td>
<td>31.7</td>
<td>25.5</td>
</tr>
<tr>
<td>% IQR &lt; 2.2 mmol/L</td>
<td>/</td>
<td>0.04</td>
<td>0.11</td>
</tr>
<tr>
<td>Number of patient with min(BG) &lt; 2.2 (k)</td>
<td>207 (8)</td>
<td>10 (5.5)</td>
<td>24 (8)</td>
</tr>
<tr>
<td>Median IQR glucose rate (g/h)</td>
<td>/</td>
<td>6.1 (6.1, 6.1)</td>
<td>6.1 (6.1, 6.1)</td>
</tr>
</tbody>
</table>

Figure 1 – BG empirical cumulative distribution function reported clinically (NICE-SUGAR), for STAR simulations (STAR) and NICE-SUGAR simulations (NS-3H), and NICE-SUGAR 3-hourly protocol (NS-3H).

Conclusion

Glycaemic control protocols need to be both safe and effective for all patients before potential clinical benefits can be assessed. NICE-SUGAR clinical results do not match results expected from their protocol, and show reduced safety and performance in comparison to STAR.