Inducing hypoglycemic episodes reliably and safely with the automated glucose clamp technique

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INTRODUCTION

Hypoglycemia represents a major challenge in the management of diabetes. Therefore, the accuracy of continuous glucose monitoring (CGM) systems in the hypoglycemic range is of particular interest to enable systems to reliably detect low blood glucose (BG) levels and prevent severe hypoglycemia.

In clinical studies hypoglycemic events often occur infrequently and randomly making standardized evaluation protocols for CGM systems difficult. Therefore, it has been proposed that at least 7.5% of data points in performance studies should fall within the hypoglycemic range (defined as < 70 mg/dL) [1], to ensure sufficient representation of this clinically relevant zone.

To date, delayed and elevated insulin administration in combination with meals have been commonly used to induce hypoglycemia in clinical studies. While this method is relatively simple to implement, the resulting glucose profiles are highly dependent on meal composition, insulin dosage and timing, which limits reproducibility and standardization.

We therefore investigated if hypoglycemia could be safely and reliably induced with the automated glucose clamp technique. ClampArt is a CE-marked device specifically developed for conducting glucose clamp studies. ClampArt allows reliable and reproducible establishment of BG concentrations at predefined target levels including hypoglycemia through automatically calculated and administered glucose infusion rates.

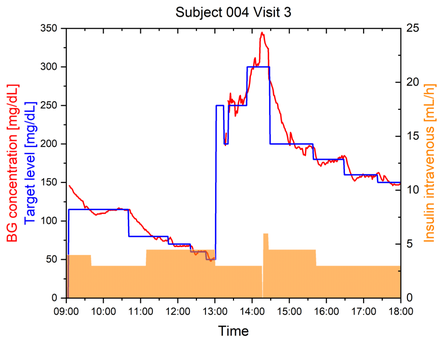
METHODS

Data of two different clinical studies conducted using the ClampArt device were analyzed with respect to manageability and safety of intentionally induced hypoglycemic episodes.

Both studies included participants with Type 1 diabetes. In the first study, six subjects underwent two clamp procedures each. The second study involved eleven subjects, of whom ten participated in two and one in a single clamp experiment.

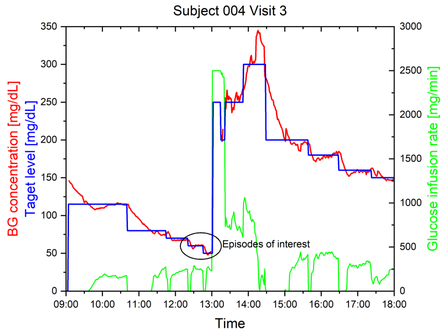
Both studies involved varying target levels of the participants' BG concentrations. To achieve this, the ClampArt device was programmed to variable glucose target levels. The algorithm responsible for the automatic regulation of BG concentration calculated the necessary glucose infusion rates accordingly. During the clamp sessions, different intravenous insulin dosages were administered continuously to reduce BG levels as required and generate the option of regulating the glucose concentration (figure below).

The design of both studies included episodes of hypoglycemic glucose concentrations. In the first study, there was one episode in each clamp with a glucose target of 60 mg/dL, lasting approximately 30 minutes. In the second study, two hypoglycemic targets were established, first at 60 mg/dL followed by 50 mg/dL. In case of intolerable symptoms or safety concerns, BG was immediately increased to levels outside the hypoglycemic range.

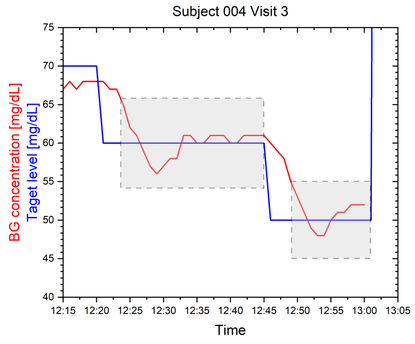


METHODS

In order to analyze the hypoglycemic episodes, we separated each episode and evaluated several characteristics. In the figure below an exemplary clamp from study 2 with two hypoglycemic episodes with 60 mg/dL and 50 mg/dL is shown.



Following the reduction of the target level, BG concentrations decreased as a result of insulin activity, in the absence of effective feedback control despite variations in glucose infusion rates. Feedback control was considered effective when BG levels remained within ±10% of the pre-defined target concentration. In the figure below, the analyzed phases are highlighted by light gray rectangles.



RESULTS

In total there were 32 episodes with a target level of 60 mg/dL and 21 episodes with a target of 50 mg/dL. In three episodes, the insulin infusion was insufficient to establish hypoglycemic glucose levels. Therefore, clamp quality parameters were determined for the remaining 50 episodes as shown in the table below.

	BG target 60 mg/dL	BG target 50 mg/dL
Number of episodes	32	21
Number of episodes without BG within target range	2	1
Mean (±SD) duration of control [min]	29.4 ± 11.1	14.0 ± 9.5
Mean (±SD) precision [mg/dL]	2.8 ± 1.0	2.5 ± 1.1
Mean (±SD) control deviation [mg/dL]	0.3 ± 2.2	0.4 ± 2.7
Mean (±SD) absolute control deviation [mg/dL]	3.1 ± 1.9	2.9 ± 1.5

During the hypoglycemic episodes, participants were continuously monitored by clinical staff. As the low BG concentrations were intentionally induced, associated hypoglycemic symptoms were not classified as adverse events. We analyzed the frequency and duration of unintentionally low BG levels as safety marker for the hypoglycemia management through the ClampArt system.

Safety parameters Target level 60 mg/dL	
Number of clamps with BG < 54 mg/dL	7
Mean (±SD) duration with BG < 54 mg/dL [min]	1.5 ± 5.5
Number of prematurely terminated episodes	0

In the table above the results for hypoglycemic episodes with the target level of 60 mg/dL are shown. In 7 from 32 experiments, BG concentration fell below 54 mg/dL. None of the clamp procedures were terminated prematurely due to intolerable symptoms or other health-related complications.

RESULTS

The table below presents data on hypoglycemic episodes with the BG target level of 50 mg/dL. In none of the 21 hypoglycemic episodes were BG concentrations lower than 40 mg/dL measured. However, in 3 experiments, BG concentrations fell below 45 mg/dL.

Safety parameters Target level 50 mg/dL	
Number of clamps with BG < 40 mg/dL	0
Number of clamps with BG < 45 mg/dL	3
Mean (±SD) duration with BG < 45 mg/dL [min]	0.9 ± 2.7
Number of prematurely terminated episodes	4

Prematurely terminated episodes were identified in cases where glucose infusion rates were manually increased despite no change in the predefined BG target level. In 4 instances, such premature increases in glucose infusion rates were observed. Nonetheless, minute-by-minute monitoring of BG concentrations did not reveal any critical deviations. Clinical staff responded proactively based on clinical signs, adjusting glucose infusion rates as a safety measure. Accordingly, continuous monitoring is crucial for subjects exhibiting values in these low BG concentration ranges.

CONCLUSIONS

The use of the ClampArt device represents a sophisticated method for inducing hypoglycemic episodes in a controlled and unbiased manner. Owing to its automated minute-by-minute measurement of BG concentrations, a large amount of glucose data in the low BG concentration range can be collected within a short period, thereby minimizing subjects' exposure to hypoglycemic BG concentrations.

The automated clamp technique with ClampArt can induce hypoglycemia

- reliably and reproducibly
  - Small deviations from target with little BG variation
- safely (lower than intended BG values)
  - Deviations of more than 10% below BG target are rare and last less than 2 minutes.
  - Continuous BG monitoring allows staff to reliably assess subjects' risk and to rapidly react to symptoms, if needed.

[1] Eichenlaub M, Pleus S., Rothenbühler M., et al. *Comparator Data Characteristics and Testing Procedures for the Clinical Performance Evaluation of Continuous Glucose Monitoring Systems.* Diabetes Technology & Therapeutics 2024; 26(4): 263-275

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